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# PART 1

# CLINICAL PAPERS

Extracted from the American Journal of the Medical Sciences, August, 1910

# SKIN RASHES IN TYPHOID FEVER.

By John Phillips, M.B.,

ASSISTANT PROFESSOR OF MEDICINE IN THE WESTERN RESERVE UNIVERSITY, CLEVELAND, OHIO.

The usual cutaneous manifestation seen in typhoid fever is the presence of rose spots in the form of a maculo-papular eruption appearing on the abdomen. The lesions are pale red at first, later become darker, and appear about the end of the first week, coming out in successive crops. They are usually few in number, but in some patients form a profuse eruption, covering the entire body and extremities, and are occasionally seen on the face. Sometimes the lesions are capped by tiny vesicles, at other times they are hemorrhagic. The other cutaneous lesions seen in typhoid form a very interesting group. Among these may be mentioned herpes, urticaria, sudamina, desquamation, erythema, erysipelas, purpura, furunculosis, abscess, carbuncle, impetigo, onychia, infected sebaceous cyst, decubitus, tache bleuâtre, and lineæ atrophicæ. The following description of these conditions is based on a review of the literature, and on a study of their occurrence in 1230 cases of typhoid fever, occuring in the medical services of Drs. Powell, Lowman, Upson, Cushing, and Hoover, at Lakeside Hospital; to these gentlemen I am indebted for the privilege of making this report.

Herpes were observed in 12 cases. In 8 cases they appeared on the lips during the first week of the disease. In the other 4 cases the herpetic eruption appeared late in the course of typhoid and in various regions of the body. In 1 case, a female, aged thirty-two years, a number of vesicles appeared on the forty-fourth day of her illness, a short distance outside the external canthus of her left eye and also directly above this near the hair line. Another patient, a boy, aged fifteen years, on the thirty-third day of the disease, had a small patch of herpes develop on the lower part of his chin, to the right of the median line. The third case, a male, aged fifty-two years, was afflicted with herpes over the left malar bone on the thirty-first day of his typhoid. In the fourth case, a male, aged twenty-nine years, symmetrical patches of herpes appeared on the inner and outer side of each knee, the patches on the left being more extensive. Many think that the presence of herpes labialis excludes the diagnosis of typhoid fever. That this is incorrect is shown by the 8 cases mentioned above. McCrae[1] found 20 cases of herpes in his series of 1500 patients with typhoid fever. Zinn[2] met this condition in 5 per cent. of 190 cases in the hospital at Nuremberg.

Urticaria was present in 21 cases. In some the urticarial eruption developed as a few scattered wheals on the chest or abdomen, preceding the appearance of the rose spots; in other cases it appeared later in the disease. Occasionally the lesions may cover the greater portion of the body and extremities. Miller[3] found urticaria in 2 cases in his series of 350 patients. It was formerly thought to be due to the administration of quinine, but this drug was not used in any of our patients.

A miliary eruption of sudamina is a very frequent occurrence in the third and fourth week of typhoid, when sweating is profuse. They are due to the retention of sweat drops beneath the epithelial layer of the skin. De Lacaze[4] believes that sudamina possess a definite prognostic significance. When they appear in the third or fourth week they indicate the entrance into active convalescence. My experience confirms this statement. They are usually seen on the chest and abdomen and in some cases present a striking appearance as though the skin was covered with tiny drops of water. Sudamina were present in 11 of a series of 100 cases in which a careful watch was made for this condition. Sometimes as a result there is profuse desquamation.

Quite extensive desquamation of the skin was noted in 83 patients. Riesman[5] has classified desquamation under the following heads: (1) Following vesicular rose spots, (2) as a result of sudamina, (3) an atrophic change analogous to shedding of hair, which usually appears in cases with severe fever. To this I would add a fourth, which would include those cases of desquamation which follow an erythematous eruption in typhoid. Rolleston[6] has reported a remarkable case of desquamation of the skin in large flakes in typhoid fever in a boy, aged ten years, who, on the fourteenth day of illness, had peeling of the skin off the thorax, thighs, and abdomen in flakes the size of a shilling. His heels and toes peeled in small scales. No cause for the peeling could be ascertained. Diehl[7] has reported an interesting case of exfoliative dermatitis in a male, aged eighteen years, who, during convalescence from an attack of typhoid fever, had a rash, consisting of minute, pin-head sized, bright red papules, appear on the wrists, and later spread to the dorsal surface of the hands and forearms up to the elbow. Later it spread to the feet, legs, and body. Intermingled with these lesions were a number of blebs the size of a half dollar. Desquamation followed in the order in which the eruption appeared.

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[1] Modern Medicine, edited by Osler and McCrae, ii, 117.

[2] Münch. med. Woch., 1895, xlii, 486.

[3] International Clinics, vol. iii, Sixteenth Series, p. 60.

[4] Revue de méd., 1887, p. 275.

[5] Amer. Jour. Med. Sci., January, 1904.

[6] Trans. Clin. Soc., London, 1889–1890, xxiii, 84.

[7] Jour. Cut. and Genito-urin. Dis., 1898, xvi, 222.

Of the accidental skin rashes in typhoid, probably none has received as much attention as the erythemas, because of the close resemblance at times to scarlatina and the resulting difficulties in diagnosis. The first to call attention to the scarlatiniform erythema in typhoid was Murchison,[8] who stated that in many cases of enteric fever the appearance of the rose spots is preceded, for two or three days, by a delicate scarlet rash, all over the body, disappearing on pressure. He mentions the fact that Jenner relates an instance in which this rash coexisted with slight sore throat, and the disease was mistaken for scarlet fever. Murchison states that several similar instances had come under his own observation, and even goes so far as to assert that scarlet fever appears to predispose to typhoid fever. Various other writers—Graves,[9] Ohmann-Dumesnil,[10] Moore,[11] Osler,[12] Griffiths,[13] Russell,[14] Fisher,[15] and Da Costa[16]—have called attention to the presence of a scarlatiniform erythema in typhoid. The bright red eruption may be limited to the flexor surfaces or it may cover the entire body, as in one of my cases. As a rule, there is no involvement of the throat, although Da Costa has reported a case in which there was some soreness and redness of the throat. This, as a rule, has no particular significance, as occasionally the onset of typhoid is ushered in by tonsillitis. Whipham[17] has recorded a similar case in a male, aged thirty-six years, who, on the fourteenth day of his illness, developed a sore throat, with a bright erythematous eruption over the entire trunk and a less definite rash on the legs and arms. He died four days later, but his erythema had almost entirely faded before his death. Moore attributes the development of the scarlatiniform eruption, when it appears early in the course of typhoid, to a reactive inhibition of the vasomotor system of nerves; when it appears in the third week to a septicemia or secondary blood poisoning. The diffuse erythemas are usually present in the severe toxic cases, and it seems to me that they are due to an attempt of nature to get rid of the toxins through the skin; these irritate the skin, producing an erythema just as one sees in uremia, septicemia, or in cases of intestinal auto-intoxication. In reviewing the cases of this character published in the literature, one is surprised at the number that are fatal. Seven of the cases in our series showed erythema; in one it was of the type of erythema multiforme, which developed on the back and about the buttocks.

[8] Treatise on Continued Fevers of Great Britain, second edition, 1873, p. 515.

[9] Medical Record, 1890, xxxvii, 118

[10] Jour. Amer. Med. Assoc., 1890, xv, 164.

[11] Dublin Jour. Med. Sci., 1888, lxxxvi, 497.

[12] Johns Hopkins Hospital Reports, "Studies in Typhoid Fever," i, ii, iii, 471.

[13] Lancet, 1893, ii, 1307.

[14] Lancet, 1896, i, 766.

[15] Brit. Med. Jour., 1893, i, 794.

[16] Trans. Assoc. Amer. Phys., 1899, xiv, 89.

[17] Trans. Clin. Soc., London, 1882–1883, xvi, 150.

Osler[18] has reported one case of erythema nodosum, in which the characteristic eruption on the legs appeared on the fifteenth day of typhoid fever.

A number of cases have been reported in which true scarlet fever has developed during the course of typhoid. Sequeira[19] and Caiger[20] each have met with two such cases, and Payne[21] with one case. Griffiths[22] had the remarkable experience of seeing four children in one family who were attacked by both diseases, the onset of both fevers being almost simultaneous. Cosgrove[23] has reported five cases in which the two diseases occurred in the same individual. Carmichael[24] mentions the case of a boy, aged six years, who, after suffering from scarlet fever and going on to the stage of desquamation, continued febrile from oncoming typhoid fever. Coombs[25] and Gabe[26] have each reported a similar case.

Closely allied to the cases of typhoid complicated by erythema are those which show a rash resembling measles. Instances of this kind have been reported by Beevor,[27] Neumann,[28] and Da Costa. Beevor's patient was a probationer nurse, who, on the third day of her typhoid, had a morbilliform eruption appear on her feet, legs, chest, and upper extremities. There was no coryza or conjunctivitis, nor was the arrangement of the lesions crescentic. These two facts and the appearance of the eruption on the body in a different sequence from that seen in measles, would assist in making a correct diagnosis. In this case the rash gradually faded and was not followed by desquamation. In Neumann's patient the morbilliform eruption appeared in the third week; Da Costa's two cases also developed the rash late in the course of typhoid. The co-existence of typhoid fever and measles in the same patient has been reported by Chrystie,[29] Matiegka,[30] Ringer,[31], Ringwood,[32] and Da Costa. In the two cases reported by Da Costa there was a definite history of exposure to measles, the eruption showed the characteristic crescentic arrangement, and was preceded by coryza and conjunctivitis.

In six cases purpura was noted. One of these, a girl, aged eighteen years, developed on the twenty-third day of typhoid a purpuric spot on the second toe of the left foot; this was followed by a number of petechiæ on the outer side of both feet. A few days afterward she had hematuria and menorrhagia. She succumbed from weakness and toxemia two weeks later. Four other patients had, in the third and fourth week of the disease, petechial spots appear on the lower extremities. I have not included here the cases in which there were hemorrhagic rose spots; this condition is not very uncommon. The sixth case of purpura is so remarkable that I shall give it in detail. This patient, a female, aged eighteen years, was admitted to Lakeside Hospital May 9, 1903, with a typical history of typhoid fever, with rose spots, enlarged spleen, and a positive Widal reaction. On the sixth and seventh days after admission she had two copious intestinal hemorrhages. At the same time several large purpuric spots appeared on the abdomen—one just above the pubis and another at the site of an old appendiceal scar being much larger than the others. There were also a few petechiæ over the anterior surface of the left ankle, one over the second toe of the left foot and a small ecchymosis over the great toe of the right foot. The patient complained of some burning in the ecchymotic areas of the abdomen. This was relieved by the application of hot compresses. In the course of a few days the ecchymoses on the abdomen became much darker in color, and at the end of a week a central slough had separated, leaving a ragged ulcer in the region of McBurney's point, and another just above the pubis (see Fig. 1). The patient died three weeks after admission from toxemia.

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[18] Johns Hopkins Hospital Reports, "Studies in Typhoid Fever," p. 473.

[19] Brit. Med. Jour., 1891, i, 586.

[20] Lancet, 1894, i, 1137.

[21] Ibid., 1894, p. 1264.

[22] Ibid., 1893, ii, 1307.

[23] Brit. Med. Jour., 1897, i, 29.

[24] Lancet, 1894, i, 246.

[25] Brit. Med. Jour., 1897, vol. i.

[26] Ibid., p. 848.

[27] Ibid., 1883, i. 956.

[28] Centralbl. f. klin. Med., 1890, xi, 465.

[29] Univ. Med. Mag., December, 1888

[30] Prager med. Woch., September 25, 1889.

[31] Lancet, June 30, 1889.

[32] Ibid., July 7, 1889

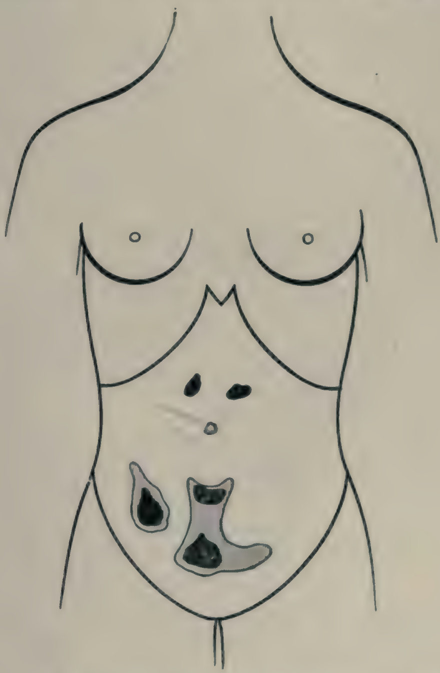

Fig. 1.—Showing the areas of ecchymoses on the abdomen. The darker areas represent the ulcers after sloughing.

Such superficial gangrene of the skin is very rare. Taupin[33] mentions a case of sloughing of the thighs, sacral region, knees, elbows, and of the face, in a child with typhoid fever. The skin became violaceous in appearance, and mortified, and this was accompanied by increase in the delirium. Hare and Beardsley[34] have reported a case in which the gangrene developed on the inside of the left calf of a girl, aged nineteen years, who had suffered some days before from a series of profuse hemorrhages. Two brown ecchymotic spots formed on the heels, but did not slough. The separation of the slough was accompanied by loss of power and sensation in the anterior part of the leg, evidently from peripheral neuritis. A very extraordinary series of ten cases of gangrene of the skin has been reported by Stahl,[35] which occurred in soldiers. Two cases in children have been reported by Jacobi,[36] and Abt.[37] McFarland[38] has also reported a series of patients in which gangrene of the skin resulted from typhoid fever. Nicholls[39] has recorded four cases in which late in the disease the hemorrhagic diathesis developed, the patients having hemoptysis, hematemesis, and hemorrhages from the bowels. A somewhat similar instance is reported by Hughes and Levy.[40]

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[33] Jour. des Con. méd.-chir., 1839, No. 7 (quoted by Hare and Beardsley, p. 177).

In four patients a pemphigoid eruption was present. In one, a girl, aged seven years, a single large bleb appeared on the dorsum of the right hand. Cultures from the contents of the bleb showed Staphylococcus pyogenes aureus. In a second case a large bulla, surrounded by a red areola, appeared on the left shin, below the knee. The third case had two bullæ, one on the dorsum of the left hand, the other in the left axilla. In the fourth patient there were two bullæ, the size of a dime, on the right buttock. In all these patients the eruption appeared in the third and fourth week of the typhoid. Osler[41] has reported one similar case.

Two cases of erysipelas occurred in this series. This complication is seen late in the course of a typhoid, when the resistance of the patient is very much reduced. The first patient, a man, aged twenty-seven years, developed during the third week of his typhoid an erysipelatous eruption on the cheeks, with a marked rise in temperature, chills, and leukocytosis. The eruption spread over the face and scalp, and after running its usual course, he recovered. The second patient, a male, aged twenty years, in the fourth week of typhoid fever, following a purulent otitis media, was afflicted with erysipelas, beginning over the right parotid. It spread so as to involve the face and the greater part of the scalp. He made a good recovery.

Curschmann[42] claims that the principal reason that erysipelas is more common late in the course of typhoid, and during convalescence, resides in the fact that at this time bedsores and other ulcerative processes form a favorable starting point for this complication. Among 1420 cases Liebermeister[43] saw erysipelas occur in ten. Of these, eight had facial erysipelas; in the other two, the disease developed about bedsores. Griesinger[44] noted fatal erysipelas in 2 per cent. of 500 cases observed at Zurich. Hare and Beardsley[45] have reported three cases of facial erysipelas in women, complicating typhoid, that occurred within a period of six weeks of each other in the wards of St. Agnes' Hospital. The first case was separated from the second by an interval of five weeks, and the second from the third by less than a week. They were all in the same ward but occupied beds at least twenty feet apart. They all made a good recovery. In one there was chronic suppuration of the middle ear. In the collected statistics of Hare and Beardsley erysipelas was found recorded sixty-four times in 3910 typhoid patients, which is about 1 to 61, the proportion given by Gerente. Other interesting cases of this complication have been described by Thielman,[46] Berthoud,[47] Armiex,[48] Freudenberger,[49] Potain,[50] and Martine.[51] Silverstrini[52] has reported two cases of facial erysipelas in typhoid fever, in which the inflammation was found to be due to the bacillus of Eberth, and not to streptococci.

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[34] Typhoid Fever and Exanthemata, second edition, 1909, p. 177.

[35] Quoted by Hare and Beardsley, p. 178.

[36] Arch. Péd., December 15, 1899.

[37] Jour. Amer. Med. Assoc., 1901, xxxvii, 445.

[38] Quoted by Hare and Beardsley, p. 179.

[39] Montreal Med. Jour., June, 1906.

[40] Arch. de méd. et de phar. mil., August, 1892 (quoted by Hare and Beardsley, p. 179).

[41] ''Studies in Typhoid Fever,'' Johns Hopkins Hospital Reports, p. 476.

[42] Nothnagel's Encyclopedia of Practical Medicine, Typhoid and Typhus Fevers, 1901, p. 324.

There were twelve cases of bedsores. Their most frequent site is over the sacrum, although they may be found over the occiput, the vertebral spines, the spine of the scapula, the great trochanter, the tuberosity of the ischium, and even over the heels. In some of our cases the bedsores were present on admission, owing to lack of careful nursing at home. In others the patients had severe intestinal hemorrhages, so that for a few days they were moved as little as possible. It seems to me that often more harm is done by keeping the patient in the dorsal position after a hemorrhage than would result from careful movement, because of the frequent development of bedsores. In very toxic cases they are likely to occur because of the involuntary micturition and defecation.

Under the heading of septic conditions of the skin there were noted in this series 45 cases of furunculosis, 2 of carbuncle, 5 of onychia, 9 of abscess, 1 of impetigo, and 1 of infected sebaceous cyst of the head. These cutaneous infections appear in the late stages of typhoid, when the course of the disease has been much protracted and when the patient's vitality has been considerably reduced. Edsall[53] has described a series of cases of typhoid in which furunculosis occurred about the buttocks, the infection evidently being spread by the bedpan. I have been unable to establish a similar method of infection in any of our cases. Carbuncles were present in two cases, in both of which they occurred during the stage of convalescence. In the one instance the carbuncle was situated on the outer side of the left leg, a short distance above the ankle; in the other, on the back in the lumbar region. Hare and Beardsley[54] mention one case in which the patient had a carbuncle on the back, which appeared about the twelfth day of an attack of typhoid, and persisted during a relapse and well into the second convalescence.

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[43] Quoted by Hare and Beardsley, p. 253.

[44] Quoted by Curschmann in Nothnagel's Encyclopedia, Typhoid and Typhus Fevers, p. 325.

[45] Typhoid Fever and Other Exanthemata, second edition, Lea & Febiger, 1909, p. 253.

[46] Quoted by Hare and Beardsley, p. 257. [47] Ibid., p. 258. [48] Ibid., p. 257.

[49] Ibid., p. 258. [50] Ibid., p. 259. [51] Ibid. [52] Ibid.

[53] Univ. Penna. Med. Bull., March, 1904.

There were five cases of onychia; with one exception, these were in children. They are very painful, but heal readily with proper treatment. Abscesses were present in nine patients; these were in various situations over the lower third of the tibia, in the ischiorectal fossa, in the vulvo-vaginal, gluteal, axillary, alveolar folds, in the groin, and in front of the right ankle. They are usually subcutaneous, but in some cases they may extend into the muscles. Impetigo was seen in one case. In another patient there was an infected sebaceous cyst of the head.

Another form of skin manifestation in typhoid is the tache bleuâtres, which Hare and Beardsley state were first described as occurring in typhoid by Piednagel, in 1837. The majority of observers will agree with Hewetson,[55] that they are usually, if not always, associated with the presence of pediculi. I have seen them in dispensary patients suffering from conditions other than typhoid, but in whom pediculi were present. They are steel-gray spots, 4 to 10 mm. in diameter, of irregular outline, and most abundant about the chest, abdomen, and thighs.

A very unusual lesion of the skin in typhoid is the development in children and young adolescents, especially when the disease has run a very long course and when the growth in height of the patient has been very rapid, of striæ patellares. A very interesting case of this kind came under my observation. A boy, aged fourteen years, was admitted to Lakeside Hospital May 16, 1906, suffering from a severe attack of typhoid fever. The disease ran a very long course, the complications being bronchitis, intestinal hemorrhage, and relapse. During his prolonged stay in bed he became very emaciated. He lay the greater part of the time with his knees slightly flexed and the toes extended, so that the skin was stretched. On July 2 he called our attention to some reddish scars, which were irregularly situated, in front of his knees and ankles, and appeared as if a superficial incision had been made, leaving the edges gaping open. On the anterior surface of the lower third of the leg there were in all nineteen of these scars, irregularly placed, the lowest being on a level with the tip of the internal malleolus, the highest 14.5 cm. above this point. They lay transversely, and varied in length from 1 cm. to 3 cm. The average width of the striæ was 9 cm. Directly over the centre of the patella, and extending transversely, was one of these striæ, 2.5 cm. in length, 0.25 cm. in width. In the median line over the anterior surface of the lower part of the thigh, 7 cm. above the transverse scar over the centre of the patella, was a linear transverse scar, 2 x 0.5 cm. in size. Three others of varying length were situated below the one over the middle of the patella. In all there were twenty-four of these lesions on the left extremity. On the right there were eighteen striæ, situated in positions similar to those on the left, making a total of forty-two. The positions of these striæ are seen in the accompanying pictures (Figs. 2 and 3). They were a delicate pink color, in marked contrast to the surrounding skin, and were painless, causing the patient no inconvenience whatever. There were no sensory disturbances in this case. During the patient's prolonged stay in bed he grew about four inches in height, and it seems to me that the most reasonable explanation of the striæ is the stretching of the skin from the rapid growth, the vitality of the tissues being much lowered. The occurrence of the lesions in the situations referred to was due to the fact that here, from the partially flexed position of the knees and the extension at the ankles,

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[54] Typhoid Fever and Other Exanthemata, second edition, 1909, p. 177.

[55] Johns Hopkins Hosp. Bull. v, 19.

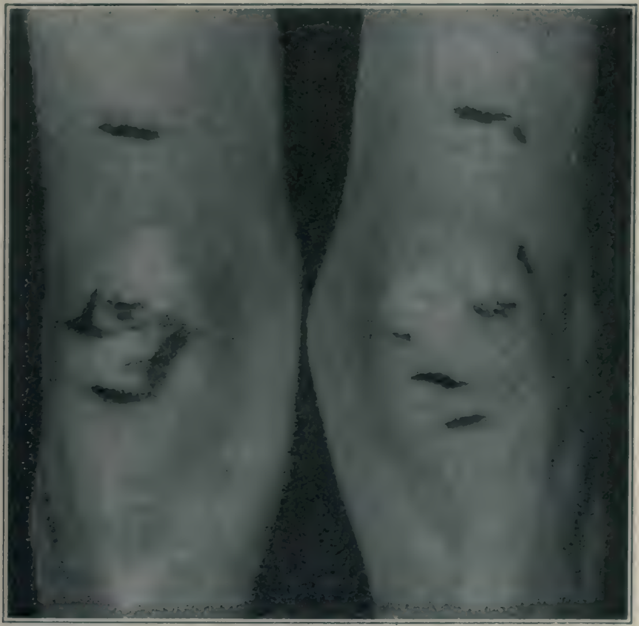

FIG. 2.—Showing the striæ about the knees.

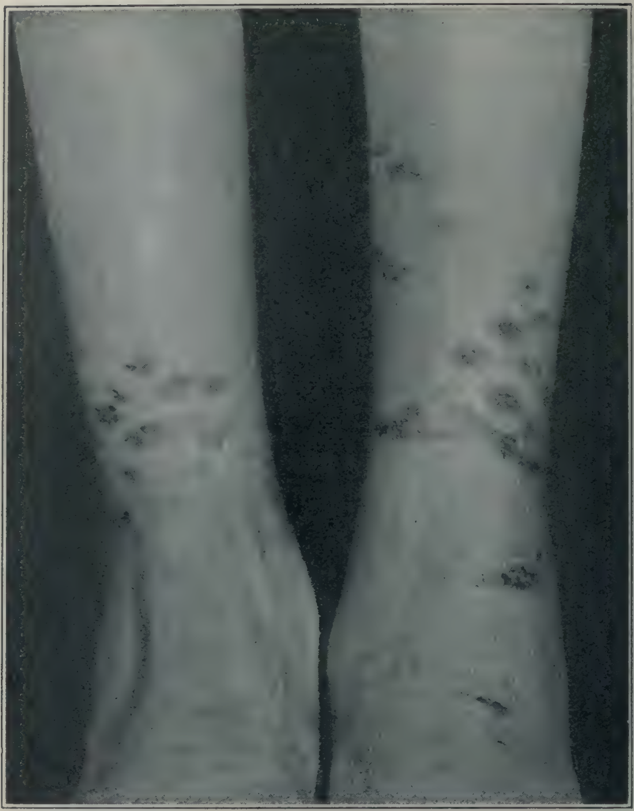

FIG. 3.—Showing the striæ above the ankles.

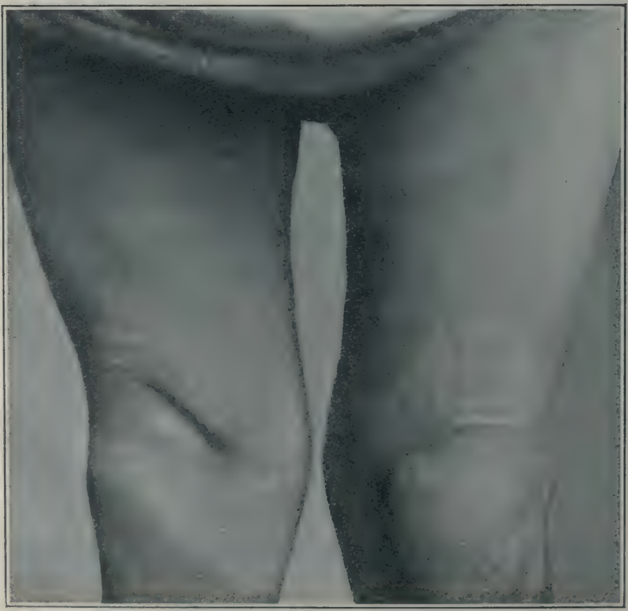

FIG 4.—Showing white, irregular, transverse scars above the patellæ.

the skin was on a tension, and, besides, the growth is very rapid at the epiphyses of the long bones.

After seeing this case, I inspected the knees, for the presence of these scars, of every patient admitted to the medical wards. Four months later I was rewarded by finding them in front of the knees of a woman, aged forty-two years, admitted for a chronic condition, and who, when fifteen years old, had been afflicted with a severe and prolonged typhoid. She had a series of white, irregular, transverse scars just above the patellæ (Fig. 4).

This unusual condition of patellar striæ was first described by Wilks[56] in the case of a lad who had been confined to bed for the greater part of the time for six years, with disease of the knee-joint. He had three transverse stripes of a pale color in front of his knee, appearing as if a piece of skin had been removed and the edges never approximated, or as if a single incision had been made and the wound, gaping open, had been filled up with some loose texture. Over the instep of the right foot were several transverse scars lying parallel with one another. Similar but less distinct scars were found on the dorsum of the left foot. No mention was made of typhoid fever in this case. Bradshaw[57] records the case of a girl, aged thirteen years, who had a severe attack of typhoid, with two relapses. On the ninety-eighth day, because of some difficulty in walking, he was led to examine the lower extremities, and found over the anterior surface of the lower third of the thighs and the patella five or six horizontal markings, the longest reaching to about one-third the circumference of the limb, and being about half an inch in width. The smallest was under an inch in length and narrow in proportion. On flexing the knee the pink portions became smooth and shiny. On placing the finger on the markings a distinct depression was felt, as if there were a crack in the true skin, filled up with a thin layer of cuticle. There were no sensory disturbances in this case.

Shepherd[58] records the presence of these striæ in a boy, aged fifteen years, with typhoid, which ran a long severe course, and was complicated by double parotitis, with paralysis of the right facial nerve, paresis of the lower limbs, and fits of an epileptic character, with a mild form of dementia. Two months after admission he had well marked striæ over both patellæ and above both knees, purplish in color and elliptical in shape, tapering to a fine point at each end. The largest was six inches in length and half an inch in breadth at the middle. Troisier[59] has noticed this complication in young adults and children. Northrup[60] describes and figures the striæ above the knees in a lad, aged seventeen years, after a protracted course of

[56] Guy's Hosp. Reports, vii, 1861.

[57] Liverpool Medico-Chirurgical Journal, July, 1888.

[58] Trans. Amer. Dermat. Assoc., 1890, xiv, 23.

[59] Bull. et mem. de la Soc. méd. des hôpitaux, 1889, No. 12.

[60] Trans. Assoc. Amer. Phys., 1903.

typhoid. He said they were at first reddish, like "welts made by a switch." Fisher[61] has recorded a case in which the striæ developed above the knees after typhoid in a girl, aged thirteen years. Sir Dyce Duckworth[62] records unilateral striæ on the thighs in a patient, aged fifteen years, following typhoid. In this case there was accompanying hyperesthesia in the distribution of the external and middle cutaneous nerves. Köbner[63] reports two cases in girls, aged thirteen and fourteen years, with the characteristic lesions in front of the knee. One of these cases he saw twenty-three years afterward, and she was found to have broad white scars at the site of the lesions. Other cases of patellar striæ following typhoid have been described by Barie,[64] Kaposi,[65] Langer,[66] Gubler,[67] Bouchard,[68] Nonne,[69] and Bunch.[70]

As seen from the descriptions given above, the most frequent site for these lesions is over the lower part of the anterior surface of the thigh and in front of the patella, though they may occur in other parts of the body and in other conditions besides typhoid. This Pflagge[71] has noticed them, after typhus fever, occurring on the abdomen, where there had been no distention of the parietes. They have been noted even on the arm and over the knuckles of the hand (Barie). Bucquoy[72] has stated that in boys these lines may have no special areas of distribution, but in girls the breasts and crests of the ilium are the places where they usually appear. With this statement I cannot agree, as no such cases have occurred in over 1300 cases of typhoid treated at Lakeside Hospital. My own case is the only one in which extensive lesions have been described over the anterior surface of the lower part of the leg and in front of the ankle. Striæ have also been described in phthisical patients and in children suffering from colitis. They always leave permanent scars because the true skin is affected.

Many causes have been given for their appearance. Barie, because there was an accompanying herpes zoster in his case, considers this conclusive of their nervous origin. In support of this Sir Dyce Duckworth found hyperesthesia of the skin in the distribution of the middle and external cutaneous nerves in his case. The most reasonable and probable explanation is that given by Bunch and others, that they are due to the stretching of the skin from excessive growth of the long bones, either from want of pressure on the epiphysis or from a juxta-epiphyseal osteitis. Bunch states that the histological changes found consist in a diminution in the interlacing of the elastic fibers and a thinning of the white fibrous tissue. The elastic fibers show a parallel arrangement which has been brought about at the expense of the crossing transverse elastic fibers which have ruptured and retracted to the edge of the lesion. In the centre of the lesion, therefore, the total number of elastic fibers was less than that found in healthy skin, and those were more or less parallel to one another. At the edge of the lesion were the broken ends of the missing elastic fibers which had retracted, and the elastic tissue here appears denser than normal. In the pars reticularis of the corium these changes were best marked, and the more slender fibrils of the elastic network seemed to have suffered most. The branching fibrils which surround the sweat glands and hair follicles tend, no doubt, when dragged upon, to cause a deflection of these glands and follicles. Troisier and Menetrier[73] have also described an alteration in the course of the bloodvessels due to the same cause, but the sections of Bunch did not show this. In addition to these changes in the corium, there was slight thickening of the prickle cell layer, but the lesion was essentially one involving the corium more than the papillary layer and prickle cells. There was some round-cell infiltration around the bloodvessels. Kaposi, however, has examined the skin in those cases and found the epidermic layer and the mucous layer much atrophied. The papillæ had entirely vanished. Langer asserts that these lesions are not due to rupture but to disarrangement of the connective tissue. The connective tissue bundles form rhomboid meshes which, when the integument is distended, stretch most readily in the long axis. He says the striæ are the result of violent stretching, the bundles in part becoming parallel and remaining in position.

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[61] Münch. med. Woch., 1904, 482.

[62] Brit. Jour. Dermat., 1893, p. 357.

[63] Münch. med. Woch., 1904, p. 928.

[64] Sem. méd., 1888, p. 259.

[65] Diseases of the Skin, Hebra, vol. iii, 262.

[66] Anzeiger der k. k. Gesell. der Aerzte in Wien, No. 28, 1879.

[67] Quoted by Bunch, Brit. Jour. Dermat., 1905, xvii.

[68] Ibid.

[69] Ibid.

[70] Brit. Jour. Dermat., 1905, xvii.

[71] Zeitschr. f. die Staatsarzneikunde, 1861, xv, 369.

[72] Quoted by Hare and Beardsley.

[73] Arch. de méd. expér., 1889, p. 134.

No. II.

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# Report of a Case of Hodgkin's Disease with Recurrent Fever. A Study of the Literature of this Condition.

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In Hodgkin's disease three different types of elevation of temperature have been described by Gowers.[1] In the first type the temperature is continuously raised, presenting very slight diurnal variations of a degree or a degree and a half. The highest temperature is sometimes in the morning, sometimes in the evening. The degree of elevation is usually from 100° to 103°. The second type is characterized by morning remissions, the temperature being always higher in the evening than in the morning. The daily variations are from one to three degrees, the morning temperature being at or below 100°—sometimes even normal, and the evening temperature varying from 101° to 103°. The third type is marked by periods of pyrexia in which for several days a high temperature is maintained, the daily variation being slight. Alternating with these pyrexial periods are intervals of several days, in which the temperature is normal or slightly subnormal. The temperature during the periods of pyrexia may reach 105°. The case of Hodgkin's disease here reported belongs to the third type.

J. H., male, aged 17, was admitted to the surgical wards of Lakeside Hospital, Sept. 21, 1904, because of a swelling of the glands on the left side of his neck. The family history threw no light on the case. None of his relatives had ever suffered from tuberculosis. He does not remember having had any of the diseases of childhood or any other illness but he has always been rather weak and delicate. He denies venereal infection. His present illness dates from February, 1904, when he noticed that his collar was too small and that his neck was larger on the left than on the right side. Since then it has gradually increased in size. The swelling came first in hard lumps but these seemed to grow together. There has been no loss in weight. Physical examination at that time revealed a large diffuse swelling on the left side of the neck extending from the ear downwards to the clavicle. On palpation this mass consisted of a number of hard rounded bodies, the largest being just above the clavicle. No note was made of the condition of the other superficial lymphatics and nothing abnormal was found in the rest of the examination. His neck measured 18 inches at the base. An operation was performed for the removal of the tumor mass by G. W. Crile. An incision five inches long was made extending from just below the ear downwards to the middle of the clavicle. The sternomastoid muscle was divided and the tumor exposed. It was shelled out in large rounded pieces, the largest being removed from the lowest part of the neck, where it extended inferiorly behind the left clavicle. The wound healed by first intention and x-ray treatment to the scar was given until his discharge from the hospital on October 15, 1904. His highest temperature before the operation was 99.5°. On the two days following it was 101.8° and 101°; after that the temperature remained normal.

Examination of the excised glands showed the appearance described as characteristic of Hodgkin's disease. On section the glands were grayish, translucent in appearance and showed no evidences of suppuration. Microscopically there is noted a disappearance of the germinal centers. The capsule of the gland is thickened and there is considerable increase of the fibrous stroma of the gland. There are very numerous epithelioid cells, with a large nucleus and a small amount of granular protoplasm. Some of these cells are elongated; others take on the type of giant cells with a single large nucleus or with many large nuclei. There is a diminution of the cells of the lymphocytic type, and an increase of the eosinophilic leukocytes.

He was readmitted to the hospital on the medical service, October 26, 1905, complaining of fever, pain, and swelling of his neck. Six weeks after leaving the hospital the glands in his neck again began to enlarge and they were slightly painful. Since then his neck has gradually increased in size. At times he has felt feverish in the afternoon for several days. At other times he would feel apparently well and have a good appetite. He has lost 15 pounds in weight.

Physical examination: Patient was poorly nourished and somewhat cachectic looking, with considerable pallor of the skin and mucous membranes. He looked very ill. His tongue was coated and tremulous; there was no enlargement of the tonsils. The thyroid gland was not enlarged. All the superficial lymphatic glands were enlarged but especially those on the left side of the neck. Here, on a line corresponding to the sternomastoid muscle, there was a marked tumor, over which was the scar of an old incision, running from just behind the angle of the jaw to the middle of the left clavicle. The tumor was slightly movable and consisted of quite hard, nodular masses, which were evidently enlarged lymphatic glands. The glands on the right side of the neck in the same region were also considerably enlarged. His lungs and heart were normal. His pulse rate was 120; his blood pressure 110 mm. Hg. His abdomen was soft; there was no distention and no masses were felt. The lower edge of the liver was not palpable. His spleen was palpable and rather hard. There was no edema of the extremities and his tendon reflexes were normal.

His treatment consisted of soft diet, rest in bed, Fowler's solution, m. IV, and tinct. ferri chloridi, m. XV, after meals. During the time the patient was in the hospital he had three periods of fever, the average duration of which was 14 days, alternating with three afebrile periods the average duration of these being 10 days. During the febrile periods the temperature gradually ascended until it reached 103°, sometimes 103.5°, then fell somewhat more rapidly to normal. During the febrile periods his pulse would rise, he would feel quite ill, and the glands and spleen would enlarge. In the apyrexial intervals the patient would feel quite normal, and the glands and spleen would become smaller. During his stay in the hospital his glands diminished considerably in size. During his last pyrexial interval he had quite severe nose bleed, which was due to an ulcer on the septum, the result of an atrophic rhinitis. Several examinations of the urine were made and it was always found normal. The following blood examinations were made:

October 26, 1905 (pyrexial period), red corpuscles 4,200,000; white corpuscles 2,500; hemoglobin 55%. The differential count showed polymorphonuclear leukocytes 71%, small mononuclears 15.5%, large mononuclears and transitionals 10.5%, eosinophiles 3%. The red corpuscles stained well, showed little variation in size and shape, and one nucleated cell of the normoblastic type was seen.

Oct. 29 (pyrexial period), white corpuscles 2,600; hemoglobin 50%.

Nov. 16 (beginning of pyrexial period), red corpuscles 4,100,000; hemoglobin 45%; white corpuscles 2,600.

Nov. 19 (height of pyrexial period), white blood corpuscles 2,300; hemoglobin 44%.

Nov. 26 (apyrexial interval), red blood corpuscles 4,512,000; hemoglobin 50%; white corpuscles 2,800.

Dec. 16 (end of pyrexial period), red blood corpuscles 4,280,000; hemoglobin 43%; white corpuscles 2,100.

Dec. 24 (apyrexial interval), white corpuscles 3,800; hemoglobin 8%.

The patient left the hospital on Dec. 29, 1905, in an apyrexial interval and continued taking arsenic irregularly during the next three and a half months and was admitted again to the medical service, April 20, 1906, complaining of weakness, soreness in his legs, pain in his abdomen, and cough. Since leaving the hospital he had been at times chilly and feverish and felt quite ill, though he did not keep a definite record of these periods. He was more feverish in the afternoon and evening and at times had profuse sweating at night. Three weeks before his last admission he felt very weak and tired and became so short of breath that he could only with great difficulty go up stairs. He had some cough but had not expectorated any blood. He had also been troubled a great deal with nausea. For the previous four days he had complained of a troublesome pain in the left side of his abdomen.

Physical examination: Patient was very pale and emaciated. His hair was dry and falling out; his skin was dry and showed brownish pigmentation on the face and forehead. He looked quite ill. His right pupil was larger than the left; both reacted well to light and accommodation. All the superficial lymphatic glands were enlarged, but especially those of the neck, which were quite large and firm. Posterior to the angle of the left jaw was a distinct mass, 5x3 cm. in size, made up of individual glands. Just below this mass was the scar previously described.

The examination of the chest showed a slight diminution of resonance with increased resistance at the apex of the right lung. A few dry rales were heard throughout both lungs.

The heart was of normal size but the first sound at the base was partly replaced by a soft blowing systolic murmur. This could be heard faintly at the apex. There was some accentuation of the pulmonic second sound. The pulse was regular, rhythmic, full volume, rate 80 per minute, blood pressure 100, artery wall not thickened.

The abdomen was full and distended with distinct bulging in the left hypochondrium extending below the level of the umbilicus. The flanks were flat on percussion and a fluctuation wave could be made out so that there was evidently fluid in the peritoneal cavity. The liver was enlarged, extending from the fourth interspace to a point 5½ cm. below the right costal border in the mammary line. The spleen was considerably enlarged, hard, and firm, and extended from the sixth rib in the left axillary line to a point 17 cm. below the left costal border and anteriorly almost to the midline in the epigastrium. There was no edema of the extremities. The tendon reflexes were normal.

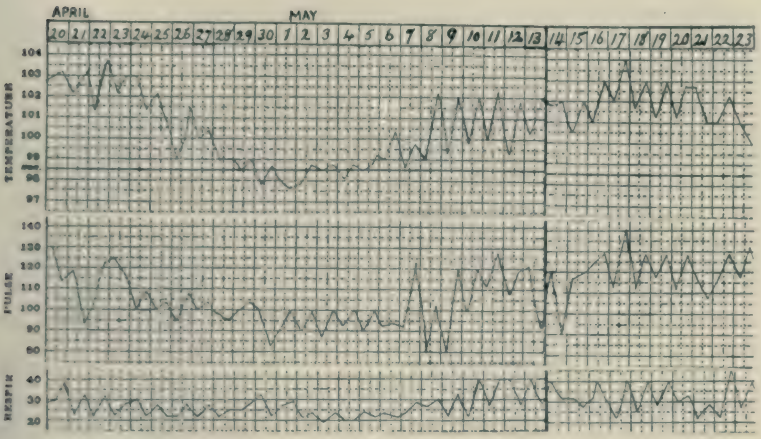
The patient was given iron and arsenic during the greater part of the time he was in the hospital but with no apparent benefit. The following notes were made of his condition: May 5, 1906, patient feels better and has had a good appetite during the past four days in which his temperature has been normal. The glands and spleen appear to have decreased in size. Amount of fluid in the abdomen about the same as on admission.

May 12, patient now having fever and feels very ill. The superficial glands everywhere have increased in size but especially the posterior cervical and posterior auricular glands on both sides. The mass posterior to the angle of the left jaw is much enlarged. Not much change in the size of the spleen can be noticed. There is evident increase in the amount of fluid in the peritoneal cavity and there is some edema of his lower extremities. Fowler's solution was discontinued because of symptoms of intolerance.

May 13, the abdomen was tapped today and 4,500 c.c. of pale olive colored fluid removed. This was quite clear, sp. gr. 1.008, alkaline, contained five grams of albumin to the liter, and did not reduce Fehling's solution. The cells were very few in number and chiefly mononuclear leukocytes. Cultures were made on various media but showed no growth. A guinea pig which was inoculated died two weeks later from some other cause, but showed no evidences of tuberculosis.

May 21, abdomen again tapped, 4,000 c.c. of fluid of the same character as that described above being removed. After the tapping a friction rub could be distinctly heard over the spleen.

May 26, patient has just finished a period of fever, during which he was very sick, with no appetite and with quite troublesome diarrhea. During this period his spleen and the glands have increased in size. Patient does not cough at all and nothing further can be made out in the lungs, than that noted on admission.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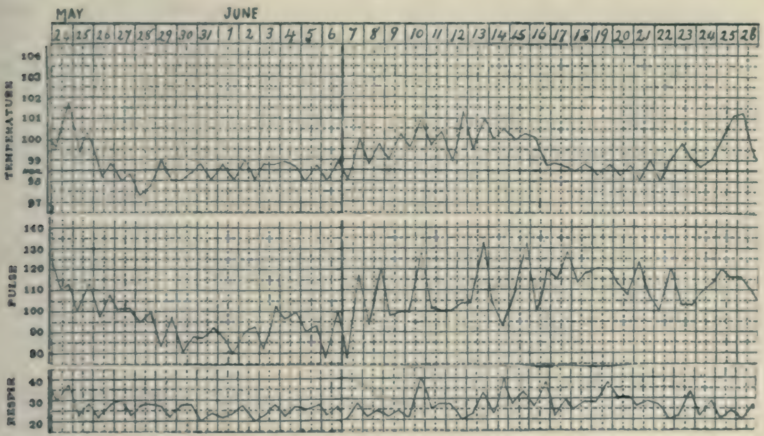
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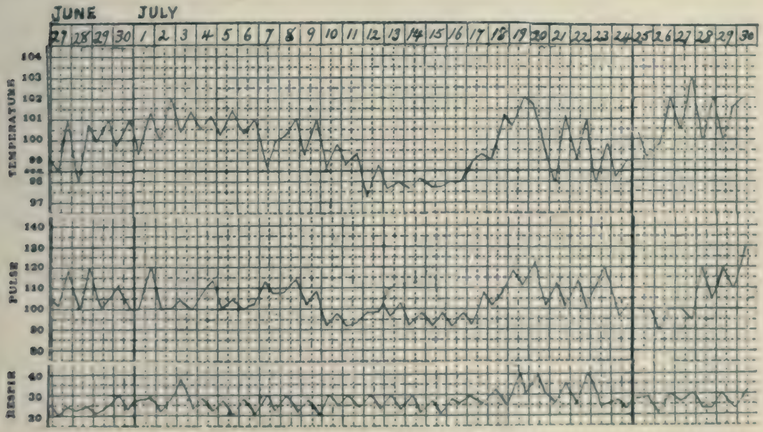
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June 6, for the past 10 days the patient has been free from fever, has felt well and has been quite cheerful. The abdomen fills up quickly so that he has to be tapped every six or seven days. The glands remain about the same in size as at the last note.

From this date until his death the patient grew gradually weaker. In the afebrile periods he would brighten up; the glands and spleen would remain stationary or slightly decrease in size; while in the febrile periods he would appear very ill and depressed, and the glands and the spleen would enlarge. During the febrile periods he sometimes had troublesome epistaxis and diarrhea. His abdomen was greatly distended, so that a paracentesis was necessary about every sixth day, six tappings in all being done. The fluid was always of the character above described. His sputum was carefully examined several times for tubercle bacilli, but none were found. He grew gradually weaker and died July 30, 1906.

The following blood examinations were made:

April 20, 1906, (febrile period), red corpuscles 2,248,000; white corpuscles 1,800; hemoglobin 28%. The differential count showed polymorphonuclear leukocytes 55.5%, small mononuclears 28.3%, large mononuclears and transitionals 15.2%, eosinophiles 1%. In the stained smear the red corpuscles showed considerable variation in size and shape, and an enlarged pale area. No nucleated red cells were seen. The Widal reaction was negative.

April 27 (near the end of febrile period), red corpuscles 2,048,000; white corpuscles 1,900; hemoglobin 30%.

May 6, (beginning of febrile period), red corpuscles 2,784,000; white corpuscles 2,300; hemoglobin 35%.

May 10 (height of febrile period), red corpuscles 2,508,000; white corpuscles 2,200; hemoglobin 35%; coagulation time 2½ minutes. The differential count showed polymorphonuclear leukocytes 50.5%, small mononuclears 28%, large mononuclears and transitionals 20.5%, eosinophiles 1%. No nucleated red cells were found.

May 18 (febrile period), red corpuscles 2,100,000; white corpuscles 3,400; hemoglobin 30%. The differential count showed polymorphonuclears 49.5%, small mononuclears 35.4%, large mononuclears and transitionals 14.1%, eosinophiles 1%.

June 6 (afebrile period), red corpuscles 3,168,000; white corpuscles 3,400; hemoglobin, 40%.

June 10 (febrile period), red corpuscles 2,904,000; white corpuscles 2,600; hemoglobin 40%.

June 18 (afebrile period), red corpuscles 3,056,000; white corpuscles 2,100; hemoglobin 40%.

June 26 (beginning of febrile period), red corpuscles 2,848,000; white corpuscles 2,800; hemoglobin 35%.

July 3 (febrile period), red corpuscles 3,328,000; white corpuscles 3,200; hemoglobin 40%.

July 4 (febrile period), white corpuscles 4,200.

July 5 (febrile period), white corpuscles 4,300.

July 6 (febrile period), white corpuscles 4,100.

July 7 (febrile period), white corpuscles 5,600.

July 8 (febrile period), white corpuscles 5,200.
July 9 (febrile period), white corpuscles 6,800.
July 10 (febrile period), white corpuscles 9,400.
July 11 (febrile period), white corpuscles 11,000.
July 12 (afebrile period), white corpuscles 10,900.
July 13 (afebrile period), white corpuscles 10,600; red corpuscles 3,832,000; hemoglobin 40%.
July 14 (afebrile period), white corpuscles 9,100.
July 15 (afebrile period), white corpuscles 9,200.
July 16 (afebrile period), white corpuscles 8,000.
July 20 (febrile period), white corpuscles 7,200.
July 21 (febrile period), white corpuscles 7,800.
July 22 (febrile period), white corpuscles 9,200.
July 23 (febrile period), white corpuscles 10,400.
July 24 (febrile period), white corpuscles 11,800.

Autopsy protocol (abstract): Anatomical diagnosis—chronic hyperplasia of the retroperitoneal, aortic, bronchial, tracheal and right cervical group of lymph glands (Hodgkin's disease); subacute perisplenitis and periphepatitis; caseous tuberculosis of two bronchial lymphatic glands; acute circumscribed inflammatory tuberculosis, associated with thrombosis, of lungs, liver, spleen, kidneys and some of the bronchial and cervical lymph glands; hydroperitoneum and edema.

The body is that of an emaciated male boy, 156 cm. long. The body heat is still present; rigor mortis is absent. Except for slight lividity of the dependent parts, the body surface is blanched. Extensive edema of the lower extremities, the back, and the scrotum is present. The abdomen is distended; between the umbilicus and the pubes, there are several scars the result of paracentesis. On the right side of the neck posterior to the body of the sternomastoid muscle, and below and behind the angle of the jaw, is a mass of glands, 6x3 cm. in size, firm, circumscribed, and movable. The axillary and inguinal glands are not enlarged.

On opening the abdomen the subcutaneous fat is practically absent; the muscles are very pale. The peritoneal cavity contains 4,820 c.c. of clear straw colored fluid; the peritoneum is whitened and thickened. The spleen is enlarged and hard and is adherent at its upper surface. The liver is also adherent to the diaphragm by means of soft, organizing adhesions. The retroperitoneal tissue is increased in amount and is dense and hard.

The heart is of ordinary size and appearance and shows nothing abnormal. The left lung is free from adhesions. The left pleural cavity contains 180 c.c. of clear fluid. The lung is partially collapsed and is everywhere studded with small, millet-seed-sized, discrete nodules, some of which shine through the pale mottled pleura. On section both lobes are equally filled with separate small, grayish yellow nodules, varying in size from a pin point to 2 mm. in diameter, and surrounded everywhere by air-containing lung tissue. There are no conglomerate tubercles. The bronchial glands are enlarged and two of these contain cavities filled with yellow pus. They are deeply pigmented. The right lung is free from adhesions and the right pleural cavity contains 120 c.c. of clear fluid. The right lung is similar in all respects to the left. The right bronchial glands are also enlarged. The vessels are normal.

Surrounding the bifurcation and extending upwards 6 cm. on the trachea, is a mass of enlarged lymph glands which lie somewhat to the right; the largest of these measured 4 x 3 x 2 cm. The glands are all separate and are surrounded by thickened capsules, and show a slightly thickened interglandular stroma. On section the glands have a grayish translucent appearance, with here and there a whitish pin point area and a few reddish points. Some of the enlarged glands contain black pigment. They are all firm and hard and show no evidence of softening.

The cervical glands are much enlarged and form a mass 3 x 6 cm. in size posterior to the sternomastoid. This mass is composed of several discrete enlarged glands, grayish translucent on section. The capsule of the gland is thickened and there is considerable increase of fibrous stroma.

The liver measured 29 x 18 x 7 cm. and weighs 1,145 grams. The left lobe is triangular in shape and extends to the parietal wall above the spleen, being 3 cm. thick in the largest portion. The entire superior surface of the liver is adherent to the diaphragm by partially organized fibrous adhesions, and showing through the capsule everywhere are raised, grayish white, and separate areas. On section these areas appear to be distributed throughout the organ uniformly. Besides these nodules the cut surface shows a grayish yellow, translucent tissue, intermingled with brownish yellow tissue; together these make up the lobules, which are blurred and indistinct. The grayish yellow translucent tissue is everywhere distinct from the tubercles. The edge of the liver is sharp. The gall bladder is adherent, because of enlarged glands at the hilum of the liver. The bile ducts are patent.

The spleen measures 21 x 12 x 8 cm. and weighs 1,120 grams. It is mottled in color and generally smooth. The upper surface is adherent to the under surface of the left lobe of the liver by partially organized adhesions. On section the organ is firm, and is studded with grayish yellow, pin-head-sized tubercles. Scattered here and there throughout the spleen, are small gray translucent areas resembling lymphoid tissue, the largest of these being 3 mm. in diameter. The Malphighian bodies are not visible; the trabeculae are not prominent. The capsule is somewhat thickened and the pulp is pale red in color.

The left kidney measures 11 x 7 x 3.5 cm. and weighs 150 grams. The capsule strips readily leaving a mottled surface. Everywhere on the surface are to be seen small, grayish yellow tubercles, the largest of which measures 1 mm. in diameter. On section the cortex is 8 mm. wide; the striae are indistinct and the tissue anemic. Many small scattered tubercles are seen on the surface. The pelvis and the ureter are normal. The adrenals are normal in size and appearance. The right kidney measures 11 x 6 x 3.5 cm. and weighs 115 grams; otherwise it is similar in every respect to the left.

The retroperitoneal glands form a firm hard tumor extending from the pelvic brim to the diaphragm. The glands are enveloped in a dense fibrous tissue, and their capsules are thickened. On section the gland tissue is grayish yellow in color, translucent, hard, and shows several fine, yellowish areas, with now and then a hemorrhagic point in the cortex. The largest measures 4 x 1.5 x 2 cm. They are all separate and distinct, and surrounded by an increased amount of fibrous tissue.

The pancreas is partially imbedded in the glands and appears normal.

The stomach, intestines and other organs appeared normal. The brain was not examined.

Histological examination. Lymph glands: Sections were made completely through glands of medium size and through portions of the largest glands. The section of a medium sized gland, measuring 10 x 7½ mm., shows a variety of changes. The capsule is somewhat thickened and the structure of the gland is completely transformed, due to a complete disappearance of the germinal centers. The tissue is composed of cells of various sizes and types supported by a variable but never conspicuous amount of fibrous tissue. Cells of the lymphocytic type are relatively few in number. The most numerous cell is a relatively large flat or polygonal type cell with a relatively large vesicular nucleus and with a smooth or finely granular cytoplasm, which stains faintly but decidedly with eosin. Where these cells are crowded together, especially in the neighborhood of connective tissue trabeculae, they are often elongated and even of a spindle shape. These cells apparently take their origin from the so-called reticulum cells of the tissue. They undergo various transformations. Some apparently differentiate into fibrous tissue, at least they become very much elongated, the nuclei becoming denser, and they have all the appearances of young and differentiating fibrous tissue cells. Another fate is the formation of giant cells and all gradations can be traced between the flat or polygonal cells and large multinucleated giant cells. Hypertrophy of the nucleus seems to be the first step in this change. The large giant cells may have a single giant nucleus with one or many buds; exceptionally the giant cells have a number of small nuclei. These nuclei are, with few exceptions, at or near the center of such cells. In some areas there are considerable numbers of eosinophilic leukocytes. In some portions of the glands there is an apparent increase in the number of blood capillaries, in other portions an apparent decrease. There are no appearances suggestive of the histological structure of tuberculosis. The condition is evidently an inflammatory lesion of the subacute type. Exactly the same appearances are met with in sections which include a portion of the very much enlarged glands. In other glands, both large and small, in addition to the changes above described, there is a marked formation of a rather dense fibrous tissue poor in blood vessels, nearly devoid of lymphocytes, but containing variable numbers of flat and elongated cells and of giant cells in various stages of development. Eosinophilic leukocytes are not so numerous in these glands as in the first type described. Sections of several of the glands of both types show recent thrombi of both veins and arteries. The walls of some of these thrombosed vessels are infiltrated with mononuclear leukocytes and some of the thrombi are composed largely of cells which are necrotic. No definite histological tubercles are found.

Lungs: Sections of the lungs are studded with very small pneumonic areas in which the pulmonary alveoli are the seat of both an alveolar and an interstitial exudation. The alveolar exudation consists of fibrin, desquamated epithelial cells, polymorphonuclear and mononuclear leukocytes. In some places the tissue is necrotic and is undergoing caseation. Many of these areas of pneumonia are in definite connection with vessels showing recent thrombi. There are no miliary tubercles in the ordinary sense. In stained smears from the pus of the thrombi, tubercle bacilli were found.

The spleen, the liver and the kidneys show small areas crowded with leukocytes but no typical histological tubercles. These areas are usually in connection with blood vessels and many of them show caseation.

The case above described, from the clinical history and the pathological findings is undoubtedly one of Hodgkin's disease. For many years confusion has existed in regard to the pathology of this disease, some regarding it as a peculiar form of tuberculosis of the lymph glands. It is now generally conceded that in Hodgkin's disease there is a definite and characteristic pathological picture. This was described as early as 1877 by Greenfield.[2] Later, in a discussion before the London Pathological Society, Dec. 13, 1901, Butlin and Andrews[3] from an investigation, clinical and pathological, of 20 cases, gave a very clear and accurate account of the changes found in the glands and other tissues in Hodgkin's disease. Early the glands may be comparatively soft, but later they are exceedingly hard, feeling like firm fibrous tissue bound not merely to each other but to the surrounding parts. On section they are quite homogeneous, look almost like a section of brain with here and there little blotches or spots with lines of blood vessels on them. Microscopically the glands present the following changes according to Andrews: (1) The general plan of the structure of the glands is obscured and simplified; the distinction between the cortex and medulla is abolished, or nearly so, so that the whole gland has a more homogeneous appearance. (2) The number of lymphocytes is apparently very much decreased; they are proportionately scanty and no longer conceal the supporting framework of the gland. (3) In correspondence with this the framework has undergone hyperplasia, the fibrillar reticulum is conspicuous,—its increase may amount to an actual fibrosis. The endothelial cells in connection with it are more numerous and much more evident; here and there some of them attain a very large size and may contain two, four, or more large and deeply stained nuclei. These are the cells especially characteristic of Hodgkin's disease and an endothelial origin may fairly be ascribed to them. They are especially numerous in the soft rapidly growing forms of the disease; they are not always uniformly distributed, but sometimes occur numerously at special places, and sometimes large and beautiful karyokinetic figures are demonstrable in them. They have little resemblance to the giant cells in tubercle as they are not so large as the latter, they are more rounded, and their nuclei, fewer in number, are larger, stain more deeply, and occupy a more central position; their protoplasm has less tendency to degenerate changes. (4) The eosinophilic cells present in normal glands are always demonstrable in Hodgkin's disease, sometimes but not always in greatly increased numbers.

In this country similar findings were described by Dorothy Reed[4] in 1902 and later by Longcope[5] and others.

In view of the fact that our patient had a miliary tuberculosis what is the relation of the latter disease to Hodgkin's disease? The tuberculosis was evidently a terminal infection, in all likelihood having its origin in two caseous bronchial lymph glands. The tubercles throughout the different organs were all apparently recent and were all small and definitely related to a thrombosed blood vessel. It is quite conceivable that a patient with a chronic disease such as this should more readily fall a prey to tuberculosis just as one sees in other cachectic conditions, *e. g.,* diabetes. What evidence have we against the theory that Hodgkin's disease is a peculiar form of tuberculosis? Clinically the glands are harder and show no tendency to caseation as they do in tuberculosis; histologically tuberculosis of lymph glands is at first a focal lesion and the fibrosis in tubercle tends to form a capsule as it were to the diseased areas. One does not see a diffuse affection of the gland as in Hodgkin's disease. In nearly every case of tubercle the characteristic giant cells are to be found. Finally the finding of tubercle bacilli gives certain evidence that the gland is tuberculous. Inoculation of animals with portions of the affected glands in Hodgkin's disease gives negative results in a great number of cases. It has been argued that because many of the animals inoculated have died of tuberculosis that this is positive proof that Hodgkin's disease is a modified form of tuberculosis, but Pizzini has shown that 42% of guinea pigs inoculated with glands from 40 bodies dead of non-tuberculous affections showed tuberculosis, so that the finding of tuberculosis in a certain number of guinea pigs inoculated with glands in cases of Hodgkin's disease carries no weight. Since the time of Virchow many have claimed that Hodgkin's disease was a form of lymphosarcoma. Against this view it may be urged that the growth differs from malignant tumors in the absence of infiltration of the capsule and surrounding tissues, and the fact that malignant disease does not metastasize in one form of tissue only. Adami in his recent book says that to speak of Hodgkin's disease as a form of lymphosarcoma is absolutely unjustified.

The unusual feature of this case was the long continued recurrent fever, lasting nine months. In the original article in 1832 by Hodgkin[6] "On Some Morbid Appearances of the Absorbent Glands and Spleen" is described a case of this type—"Martha Newton, aged apparently about 25 years, a patient of Dr Bright's in Dorcas's ward, into which she was admitted on the 17th instant. She had come to town from Brighton and described herself as laboring under intermittent fever but her appearance did not altogether accord with his idea of ague. She stated that she had been taking bark prior to her coming to town and a repetition of the bark or sulphate of quinine was prescribed. Her pulse was not remarkable either for quickness or irregularity, and none of her complaints suggested a suspicion of disease of any of the viscera of the thorax. She had one paroxysm shortly after her admission, which was reported by the sister of the ward to differ from the ordinary paroxysm of ague. She was seen by Dr Bright in another of these paroxysms on the 19th. The quinine bark was continued but some local or visceral disease rather than ague was suspected. She died suddenly on the morning of the 20th after eating a moderate breakfast." The autopsy proved this case to be one of Hodgkin's disease. In 1858 Wunderlich[7] described a case of this type in which he once noticed during a period of fever an increase in the size of enlarged glands and spleen with a diminution in their size when the temperature fell. In 1870 Murchison[8] reported a case of Hodgkin's disease in a girl aged six in which the enlargement of the glands appeared six weeks after an attack of whooping cough. She had periods of fever lasting 14 days alternating with apyrexial intervals lasting 10 days. In the latter periods the child appeared well, played about and had an enormous appetite, while during the periods of pyrexia the child was languid, had aching pains, and the enlarged glands increased in size and became quite tender. Nine years later Gowers called attention to the three types of temperature in Hodgkin's disease previously described and mentions a case with recurring fever that had been under the care of Wilson Fox. This case had marked increase in the size of the glands during the pyrexial period. Pel[9] in 1885 reported a case of Hodgkin's disease in a man aged 25 years who had recurring fever during the four months he was under observation. Two years later[10] he recorded two similar cases. Osler[11] also in the same year (1885) mentions one of his private cases with similar clinical symptoms. Under the title "Das chronische Rückfallsfieber eine neue Infectionskrankheit," Ebstein[12] describes the case of a mechanic 19 years old, with periods of pyrexia lasting 13 or 14 days alternating with periods of apyrexia of 10 or 11 days' duration. He had nine such pyrexial periods in 211 days. The rise in temperature was quite gradual but the fall was relatively more rapid. Ebstein also observed that the patient during the period of fever, was quite ill, lost rapidly in weight, had little or no appetite, had headache, pain in the abdomen and enlargement of the spleen. Similar cases have been reported by Hanser[13], Völckers[14], Klein[15], Stevens[16], and others. H. Batty Shaw[17] in 1901 reports a case of this type in which with the accessions of temperature, besides the local glandular changes there were rigors, anorexia, vomiting, and diarrhea. He gives an excellent résumé of the literature, analyzing 17 cases. He found that the time that elapsed between the onset of the fever and death in the cases reported varied from 2½ months to 14 months. In our case it was at least nine months.

Many attempts have been made to demonstrate microorganisms in these cases. Maffucci[18] found streptococci and bacilli in the enlarged glands. Majocchi and Pecchini[19] found a micrococcus and a short bacillus in all the parts of the body affected. Cardarelli[20] found a typhoid-like organism. Klein found streptococci in the cortex of some of the affected glands. Evidently the presence of these organisms was due to a terminal infection. Neither in our case nor in any of the cases described has a leukocytosis been found during the periods of fever. The duration of the pyrexial periods and the apyrexial intervals is of such regularity as to suggest the possibility of a definite life cycle of some organism, which might cause the temperature. Indeed the temperature charts in the cases reported resemble each other so closely that the appearance of the chart itself would at once suggest to the observer that the case was one of Hodgkin's disease with recurring fever, just as the appearance of a malarial chart would suggest malaria.

In conclusion I wish to thank Dr Edward F. Cushing for the privilege of reporting the clinical history of this case, and Dr W. T. Howard for the use of the autopsy report and for valuable assistance in the study of the pathological material.

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# RHEUMATIC MYOSITIS.

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The particular phase of the large subject of muscular rheumatism considered in this paper is the relation of certain acute inflammatory conditions of the muscles to acute rheumatic fever. Chronic muscular rheumatism was fully described so long ago as 1816 by Balfour. Rheumatic involvement of muscles was also extensively studied by the Swedes, notably by Froriep, in 1843, and Helleday, in 1876. They, however, paid more attention to the chronic nodular condition and its treatment by massage. Considerable was written about the subject of acute myositis in the German literature in a period of about five years from 1892 to 1897. A number of series of acute cases, some epidemic in character were reported and the general consensus of opinion at that time was that they were infectious and identical with acute articular rheumatism or the same in an attenuated form. Some even claimed that many of the mild cases reported as dermatomyositis were of the same nature. There is little doubt that the condition has been variously diagnosticated, as the cases to be reported later well illustrate. The English literature on the subject is scanty. In the last year several articles have appeared, but like the Swedish writings, mostly with reference to the chronic muscular conditions under the name of fibrositis or nodular fibromyositis, which is described as independent of acute rheumatism or, indeed, any acute myositis. The French literature is also scanty. However, Rose,[1] under the heading of muscular cephalalgia, although describing the chronic fibrositic condition, refers to rare acute cases, which subside under salicylates and mentions acute muscular and articular rheumatism in the etiology.

In that period of interest (1892-1897) in the German literature, when these cases of acute myositis were more recognized than at any time since, the subsequent condition of a nodular infiltration (*Rheumatische Muskelschwiele*) was repeatedly described, sometimes in cases that had definite joint and muscle involvement at the same or different times, sometimes when only the muscle was involved. The infection of rheumatic fever may not be the only cause of the recently exploited fibrositis, especially if, as was was done by Luff, one includes under that heading such obviously different fibroid processes as Dupuytren's contracture.[2] But, the first question is whether a specific rheumatic myositis exists, that is, as a local manifestation of the generalized infection of rheumatic fever, the same as arthritis, phlebitis, or iritis. Various writers have inferred that the condition was an established fact (Kerr[3]), yet in the rather detailed classification of the inflammatory conditions of the muscles in Albutt and Rolleston's series, there is no mention of it. One case is described in Osler's series.

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[1] Sem. Médicale, vol. xxxi, pp. 145, 156.

Before considering further the etiology of this condition the following cases from the Medical Dispensary of Lakeside Hospital may be reported:

Case I.—This case is so typical that it may be reported at some length. Miss L. M. came to Lakeside Dispensary for the first time in 1897 complaining of blurred vision. A diagnosis of interstitial keratitis was made, and a few ridges on the teeth were regarded as confirmatory evidence of congenital syphilis. The clouding all cleared up after about four or five months of antisyphilitic treatment. One year later the same condition recurred in the other eye. This also cleared up with the same treatment. In the summer of 1900, the patient returned to the Medical Dispensary with a painful swelling of her left arm in the upper outer part. She had never had acute rheumatism or any infectious diseases that would have any bearing on the case, except the specific keratitis. Evidently the swelling was suspected to be an abscess, as it was incised in the dispensary. There was no suppuration and the wound healed rapidly, leaving the swelling the same. She was then given a course of antisyphilitic treatment without improvement. In August of 1900 she was sent into the hospital on the surgical service. A general anesthetic was given, and a second larger incision was made. The record of the operation reads as follows: "Over the periosteum was a layer of velvety gelatinous material. An attempt to curette this away failed, so all the tissue was chiselled away, down to firm bone. The wound was packed wide open. Subsequently it was noted that there was only rather free serous discharge from the wound, and that healing took place rapidly. The swelling was still distinct, although somewhat less at the time of her discharge, August 14, 1900.

After this experience she did not return to the hospital until the fall of 1911, when she appeared at the Medical Dispensary and related the following history: She went to a physician outside who treated her arm mostly by counter-irritation over a period of six months. The condition in her arm then practically disappeared, but left some indefinite soreness, for which she had several treatments by a masseur. All symptoms then disappeared and never again recurred in the same location. Several years later she had another swelling over the upper end of the sternum which was also incised to drain a supposed abscess, but no pus was obtained. In 1901, that is, previous to the second obscure swelling, she had a typical attack of acute articular rheumatism, and in 1904 a second, and in March, 1911, a third. With the last attack the right temporal muscle and the lower third of the quadriceps extensor femoris became swollen and painful. The patient thinks these swellings were of the same nature as those of the arm and sternum. The thigh swelling subsided promptly. The right temple, however, remained swollen, indurated, and painful, and caused constant headache. After enduring this for about two weeks, she appeared at the Medical Dispensary with the temporal muscle rounding out from the zygoma to the temporal ridge prominently enough to give a rather ludicrous contour to her otherwise small narrow face. At this time there was also marked chronic endocarditis with mitral insufficiency. She was given 15 grains of sodium salicylate four times a day, but returned in a few days unimproved. She was then given 15 grains every two hours with an alkali until toxic. The pain disappeared in one day. The swelling was nearly all gone in three or four days, leaving some diffuse induration. Since then the swelling has recurred at intervals of three or four weeks, each time being relieved by salicylates. During October, 1911, the condition became more continuous and chronic, and reacted less favorably to salicylates. Since then she has been treated by massage, and is regarded as a case of indurative headache, as described by Edinger.[4]

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[2] Lancet, 1910, i, 712.

[3] Amer. Jour. Obst., vol. lxiii, p. 931.

A few other cases may be reported more briefly.

CASE II.—Boy, aged fifteen years. Mother rheumatic. Patient had measles, mumps, pertussis, and diphtheria, but no tonsillitis or acute rheumatism until the present illness, which began with sudden pain in the wrist, shoulder, and ankle. After about two days the upper half of the right arm swelled up over night, and remained so for a week or more, during which time the joint symptoms had subsided. He was then admitted to the hospital with a temperature of 101°, the right arm the seat of marked swelling of a firm elastic character, skin redness, and so much pain and loss of power that the arm lay helpless at his side. Acute osteomyelitis was considered in the diagnosis. Two $x$-ray plates were negative. The blood examination was as follows: Leukocytes, 8800; hemoglobin, 95 per cent.; Differential count: Small mononuclears, 21 per cent.; large mononuclears, 5 per cent.; polymorphonuclears, 69 per cent.; eosinophiles, 4 per cent.; transitionals, 1 per cent. He also had at this time a slight mitral insufficiency. He was rendered toxic with salicylates with prompt relief. The swelling subsided gradually. At the end of three weeks his arm was painless, but the biceps and the upper part of the brachialis anticus were rather thickened and indurated.

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[4] Modern Clinical Medicine, Diseases of the Nervous System, p. 863.

CASE III.—Mrs. M. C., aged thirty-nine years. Two weeks after the onset of acute articular rheumatism involving both knees and ankles there appeared swelling and tenderness of the upper part of both thighs, more marked on the right, also tenderness in the lower two inches of the biceps muscle and its tendon on both sides. Three days later, after being rendered toxic with salicylates, both thighs were one inch less in circumference, measured at the same level, and there was much less pain.

There have been 2 other cases less acute, but with distinct muscular swelling involving the left scapular muscles and right trapezius respectively. Also another case of indurative headache without swelling when observed, but with tenderness along the attachment of the temporal muscle.

In this connection a case may be reported from the private practice of Dr. John Phillips, with his permission. The patient was a well developed women, aged thirty years. Her general health was good and there was no alcoholic history. One year ago she had a rather mild attack of acute rheumatism with pain and swelling of both shoulders and a temperature of 101, associated with brachial neuritis and tenderness above the clavicle on the right side and tenderness over all the nerves of the arm. There was almost complete loss of power. She was put on oil of wintergreen until toxic. The acute pain subsided in two or three days, and the neuritis in two weeks, although it was five weeks before the strength in the arm was regained. At the same time she had severe headache and tenderness of the scalp, with thickening of the insertions of the sterno-mastoid and trapezius muscles of sufficient degree as to be discovered by the patient. This thickening disappeared under massage and salicylates in about 48 hours. Five months ago she had a similar condition of the muscles of the head with some weakness of the left arm and tenderness over the ulnar and median nerves. The headache again yielded to salicylates and massage. The neuritis cleared up in about three weeks. There was no endocarditis.

In the first 3 cases it seems highly probable that the myositis was only a part of the generalized infection of acute rheumatic fever. Of course, there is no bacteriological evidence of this fact, which would be difficult to prove, since the specificity of the micrococcus rheumaticus or any other organism is not established.

In this connection several convincing series of cases may be brought together from the literature. In 1894, Newton,[5] of Kent, reported an epidemic of 43 cases of acute muscular rheumatism seen within five weeks. The abdominal and lower intercostal muscles were most commonly involved, rendering respiration painful, short, and rapid. In some cases various muscles of the back, especially in the lumbar and sacral regions, were effected. The onset was acute, with fever of 100° to 104°; pulse, 80 to 100; furred tongue, headache, and the characteristic sour acid sweats of acute articular rheumatism. There were no nasal or pulmonary complications, which is of importance in making the differential diagnosis from influenza. Newton regarded the infection as identical with acute articular rheumatism for reasons, which he summarizes as follows: (1) There was no influenza prevalent at the time. (2) There was none of the subsequent depression characteristic of influenza. (3) They responded promptly to salicylates. (4) It was apparently mildly contagious, 3 cases occurring in one household. (5) There was endocarditis in 2 of the 43 cases; these were not treated with salicylates. (6) The epidemic occurred after an unusually wet summer and low in the valley of the Medway.

As stated before most of the reports of acute muscular rheumatism appeared in the German literature during the period of 1892 to 1897. Among the writers who expressed the opinion that the condition was the same infection as acute articular rheumatism, were Sahli,[6] Rosenbach, von Leube,[7] Immermann and Saccharjin.[8] Risse[9] thought, as referred to above, that some of the cases reported as dermatomyositis were really the same thing. He reports a case in a man, aged thirty-five years, who had had acute articular rheumatism with two recurrences. His parents were also both rheumatic. The illness reported began with acute rheumatism of both ankles. After one week, the right thigh and the right tibialis anticus and peroneal muscles became tender, swollen, and indurated. Salicylates relieved the acute pain but in two days the calf and the other thigh muscles and overlying skin became tense and edematous. The testicles and abdominal wall then became similarly involved, and some hiccough occurred, suggesting slight disturbance of the diaphragm. The case was also complicated with nephritis, lasting about four weeks. Risse thought the dermatitis and edema might simply be due to a more intense or virulent rheumatic infection. He also thought that the chronic condition (*Muskelschwiele*) when not traumatic, was usually referable to acute rheumatism.

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[5] Brit. Med. Jour., vol. xi, p. 651.

[6] Deutsch. Archiv. f. klin., Med., 1893, Band li.

[7] Deutsch. med. Woch., 1894, Band i.

[8] Ibid., 1894, p. 525.

[9] Ibid., 1897, p. 232.

Sick[10] reported an instructive series of 9 cases occurring in epidemic form among nurses and attendants living in the basement of a hospital. These patients were well studied clinically and by blood and tissue examinations. Symptoms were initiated in some cases with sore throat, in all cases with malaise, gastric disturbances and general indisposition, followed in one to three days by rise of temperature and pain, swelling, and a diffuse or nodular infiltration of various muscles, usually of the thighs, calves, back, or arms. The skin was not affected and the lungs were clear. There were no neurological changes. There was excessive perspiration, and one case was associated with typical articular rheumatism. This case had had one year previous to the illness in question, acute pain in the right iliac region, with fever, and was operated on for appendicitis (during the febrile stage), but the appendix was found normal. Later she had joint swellings, then this epidemic muscular involvement, at which time a mitral insufficiency was observed; and finally, following this, an attack involving joints and muscles simultaneously, both of which were relieved by salicylates. All of these cases were characterized by a strong tendency to recurrence. Blood cultures were uniformly negative. There was no leukocytosis or eosinophilia. Excised portions of muscle showed no histological change, except in one case, in which there was some clouding of the structure and slight infiltration with fine fat droplets and round cells. No trichini were found. Bacterial stains of the tissues were also negative.

Sick considered in the diagnosis here, trichinosis, dermatomyositis, Gregarinal myositis (better known to veterinary medicine), and acute rheumatic fever. The tissue examinations excluded all but dermatomyositis and rheumatic fever. Sick did not class it as a rheumatic myositis, because it did not conform to the description of that condition given by Lorenz,[11] who gives four characteristics, namely: (1) Short duration, (2) limited localization, (3) no histological changes, and (4) no infiltration of muscle. His description, however, evidently does not apply to the acute form of myositis. Although Sick classified the condition as an attenuated form of dermatomyositis, he admits the disturbing factor of an associated typical articular rheumatism in one case. The involvement of the respiratory muscles he regarded as inconsistent with muscular rheumatism, but this was a prominent feature of the cases reported by Newton, above summarized. As to dermatomyositis, the perivascular inflammation of that disease was lacking in Sick's cases.

Herz[12] also believes there were many mild cases of dermatomyositis reported at that time, which he considered identical with acute rheumatic fever. He reported 21 cases from Breslau, with

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[10] Münch. med. Woch., 1905, lii, 1092 and 1152.

[11] Jour. Exp. Med., 1898, No. 30.

[12] Deutsche. med. Woch., 1894, p. 791.

9 recoveries. Some of these cases had joint swellings, also involvement of the tendons and tendon sheaths as well as of the muscles. The skin involvement was in the form of an erythema which resembled erysipelas, and which subsided early, leaving the myositis as the prominent feature of the disease. The skin sensibility was intact, and the electrical reactions showed at most occasional diminished excitability. One of the severe cases, fatal in six days, was autopsied, and the findings reported as follows: Bronchitis and edema of lungs; a few small infarcts of the spleen, marked softening and edema of the muscles with beginning suppuration. A culture taken twelve hours post mortem showed an organism of the colon group, which Herz regarded as a secondary infection.

V. Leube[13] reported on 200 cases of muscular rheumatism from the Wurzburg Clinic. He describes its greater prevalence, in almost epidemic form, in the spring, and expresses very strongly the opinion that it is identical with acute articular rheumatism and that only the bacteriological evidence is lacking. He also speaks of the frequent muscular involvement in ordinary acute articular rheumatism, a fact which is scarcely referred to in recent textbooks. His cases usually had considerable constitutional disturbance; many, however (two-thirds of all), especially the mild ones, had no fever. He reports one-sixth of all cases as having endocarditis.

Lacquer[14] reported a case of special interest in connection with Case I reported above, from Lakeside Dispensary. It was an acute and recurrent myositis of the upper arm, which was incised on two occasions, three years apart, but there was no gross or histological change in the muscle or periosteum. This case later had typical acute articular rheumatism. Lacquer regarded the myositis as of the same origin, probably in attenuated form.

Kerr[15] says there is no doubt of the fact that acute rheumatic fever may have as its first manifestation, involvement of the abdominal musculature, and reports 3 cases all in children at some time subjects of acute articular rheumatism. For example, 1 case had a sudden onset of localized pain and swelling in the abdominal musculature, with temperature of 100.4°, which subsided under salicylates. Three months later the child had a typical attack of acute articular rheumatism. He is personally convinced that the two differently localized affections are parts of the same disease.

In conclusion, then, if one may accept genuine rheumatic myositis as a definite clinical entity, the question arises as to its relation to the recently described fibromyositis, indurative headache, etc. Undoubtedly the chronic nodular rheumatism (*Muskelschwiele*) of the German literature would fall under this heading. However, the recent articles of Telling,[16] and Luff,[17] etc., give it a wider application, and include various fibroid processes of the skeletal musculature. Telling does not think that it is a sequel to acute rheumatic fever, or that it occurs with any frequency in genuinely rheumatic cases. However, Stockman,[18] from whose article Telling and others quote as the most complete in the scanty literature on the subject, thought that acute rheumatism was one definite cause of the chronic form, and that the subcutaneous nodules of acute rheumatism frequently persisted as indurations or thickenings of fasciæ, nerve sheaths, etc. These thickenings he considered responsible for the neuralgic pains and even atrophy following acute rheumatism. He also suggested that the nodules may be definite localizations of the infecting organism, but that the treatment required to relieve the condition at this stage was different from that of active rheumatic fever. Miller[19] also described the subacute form of myositis with slight swelling of the muscle and pain on pressure and voluntary movement, and slight effusion into the subcutaneous tissues over the muscle after the myositis has subsided. Hence it seems probable that some cases of fibrositis may follow a previous acute rheumatic myositis, which may have been mild or unrecognized. All writers, English, German, Swedish, and French agree that massage is the only really efficient treatment. This should be carried out systematically and with the idea of dispersing the infiltrations.

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[13] Loc. cit.

[14] Deutsch. med. Woch., 1896, p. 442.

[15] Loc. cit.

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[16] Lancet, 1911, i, 734.

[17] Loc. cit.

[18] Edinburgh Med. Jour., vol. xv, p. 107.

[19] Trans. Med. Chir. Soc., Edinburgh, 1897–8, xvii, 198.

No. IV

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# A Study of So-Called "Spontaneous" Gangrene

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The condition known as spontaneous gangrene, that is, gangrene non-traumatic and non-infectious occurring in healthy men in the prime of life, has been the subject of much discussion by numerous observers during the last 30 years. The unusual character of the case, on which the present study is based, has seemed to us to justify a further contribution to a subject, perhaps, already overstocked. In attempting this, we have confined ourselves to cases in which gangrene was present, realizing full well that this is merely one of the numerous manifestations of obliterative disease of the vessels of the extremities, and that many, if not all, cases of intermittent claudication, erythromelalgia, and possibly Raynaud's disease fall into the same class.

The history of the study of spontaneous gangrene dates from the year 1876, when Friedländer[26] made the first careful observations on the pathology of the vessels in this condition. He considered it to be due to an obliterating endarteritis secondary to an inflammation about the small and medium sized arteries. In 1879 von Winiwarter[62], after a careful study of one case, came to the conclusion that the condition was a disease of the vessel wall taking the form of a primary obliterative endarteritis. Following these observers, Thoma[59], Zoege von Manteuffel[71], and his pupil Weiss[65], advanced the view that the condition was due to thrombosis with subsequent organization. This opinion has steadily gained ground, until in 1908, Buerger[10] proved, fairly conclusively, the thrombotic nature of the process.

The history of a typical case of spontaneous gangrene is that of intermittent claudication in which gangrene supervenes. The patient, a male, often a Russian Jew, in the prime of life, of good antecedents, and habits, and free from syphilis, complains first of pain in the feet extending up the calves of the legs. With this pain, or preceding it, may be sensations of numbness, tingling, heat, cold, or heaviness. The pain is sharp, and appears only after exertion. Accompanying it may be a dull constant ache, resembling closely the ache of flatfoot, which moreover is often present. A period of disability extending over months or years follows, till finally the patient cannot walk more than a few hundred yards. On starting out he is free from pain, but after a few steps the pain appears, and increases until further progress becomes impossible. After resting a few moments he can again proceed. Occasionally the pain becomes constant and agonizing, and the patient can get no rest. On the other hand, the process is capable of remission, which may lead to complete cessation of symptoms.

On examination of such a case in the early stages, the affected parts are cold to the touch, pale, or in the dependent position, cyanotic, and occasionally cherry red. This is the stage resembling erythromelalgia. The superficial veins show passive congestion, and when emptied by pressure, refill very slowly. Recurring attacks, resembling phlebitis of these veins due to migratory thrombosis are not uncommon. Edema is rare. The arteries of the foot and leg are always affected. Early there may be a faintly palpable pulse, but as the process advances this disappears.

The dorsalis pedis and posterior tibial are usually the first vessels affected, but in advanced cases, all the arteries of the foot, leg and thigh, including the femoral, may be pulseless. The late stage of the condition is marked by the onset of gangrene, beginning, usually, under the nail or on the tip of the great toe. This, starting as a serous or purulent bleb, slowly goes on to the formation of an indolent ulcer and subsequently to dry gangrene, which may involve all the toes and extend on to the dorsum of the foot. The march of the gangrene is slow, and the line of demarcation almost never sharply defined, the gangrene fading gently into the surrounding engorged cyanotic skin. The reflexes may be increased or diminished depending on the amount of involvement of the nerves accompanying the affected vessels. Disturbances of sensation have occasionally been observed. While the process, at the start, is usually unilateral, sooner or later the other leg is almost always involved.

We have reviewed the literature of the subject, as far as we have been able to obtain it, and have found 73 cases, which we consider undoubted examples of spontaneous gangrene. We have excluded five cases, reported as spontaneous gangrene, occurring in the arms alone, in which the history, together with the presence of cervical rib or some other definite etiologic factor, showed clearly that they did not belong to this group. These 73 cases do not represent, by any means, all those reported, as many have undoubtedly been included under intermittent claudication, the literature of which we have not attempted to review. We have analyzed these cases as regards sex, age, duration of symptoms, condition of vessels of the affected parts, condition of the urine and possible etiology. The results are contained in the following tables.

I. Sex:

| | |
|---|---|
| Male | 69 |
| Female | 4 |
| | 73 |

II. Age:

| | |
|---|---|
| Under 20 | 2 |
| 21 to 30 | 7 |
| 31 to 35 | 9 |
| 36 to 40 | 22 |
| 41 to 45 | 12 |
| 46 to 50 | 10 |
| 51 to 60 | 10 |
| Not mentioned | 1 |
| | 73 |

It is interesting to note the early age at which the condition is found, 18 or one-fourth of the entire number occurring before the age of 35, while in 52 or more than two-thirds, the condition was established before 45. The period at which the disease is most common appears to be the last half of the fourth decade; 22 or nearly one-third of the whole number occurring between 36 and 40.

III. Race:

In only 17 of the 73 cases was it definitely stated that the patient was a Jew; 14 were Japanese. In seven the nationality was not specified. How many of those mentioned as English, Germans, Austrians, and so forth, were Jews it is impossible to determine. All observers have noticed the prevalence of this condition among Jews, especially Russian Jews. It is evident, however, that the disease is by no means confined to this race.

IV. Duration of symptoms:

| | |
|---|---|
| Over 20 years | 1 |
| Over 10 years | 5 |
| 6 to 10 years | 8 |
| 3 to 5 years | 30 |
| 1 to 2 years | 15 |
| 7 months to 1 year | 2 |
| 6 months and under | 11 |
| Not mentioned | 1 |

The disease is thus essentially a chronic one.

V. Distribution of lesions:

| | |
|---|---|
| Both legs | 23 |
| Right arm | 1 |
| Left arm | 1 |
| Right arm and right leg | 1 |
| Right arm and left leg | 5 |
| Right arm and both legs | 4 |
| Left arm and left leg | 1 |
| Left arm and both legs | 1 |
| Both arms and right leg | 1 |
| Not mentioned | 5 |
| | 73 |

In the 68 cases, in which the location was mentioned, the condition occurred 53 times in the legs alone, twice in the arms alone, and 13 times in both upper and lower extremities. It is interesting, that in the 13 cases in which the arms were affected, in all but two the legs were also involved. It has generally been stated that the condition was prone to appear in the left foot. This would seem to be erroneous, as in the above cases the condition occurred as frequently in one leg as in the other. The frequency of its occurrence in the arms has never before been pointed out.

VI. Condition of the vessels:

In the following table the cases are classified according to the most proximal artery in which the pulse is lessened or absent. It is to be understood that all vessels distal to the one mentioned are involved. The discrepancy in the total in this table is due to the presence of nine cases in which the condition of the vessels in both arms and legs has been recorded.

| | |
|---|---|
| Femoral | 24 |
| Popliteal | 20 |
| Arteries of feet (dorsalis pedis and tibials) | 18 |
| Brachial | 1 |
| Radial | 9 |
| Ulnar | 1 |
| Not mentioned | 9 |
| | 82 |

In more than one-third of the cases, the pulse in the femoral and all the vessels distal to it, was lessened or obliterated, while in nearly two-thirds the vessels as high as the popliteal were involved.

VIII. Condition of the urine:

| | |
|---|---|
| Normal | 45 |
| Albuminuria | 7 |
| Transient glycosuria | 2 |
| Not mentioned | 19 |
| | 73 |

In the two cases in which glycosuria occurred, it was not present at the time of examination, but had been noted on one previous occasion.

VIII. Possible etiology:

(a) Tobacco:

| | |
|---|---|
| Moderate smokers | 5 |
| Heavy smokers | 6 |
| Enormous smokers | 2 |
| Mentioned as not excessive | 6 |
| Not mentioned | 54 |
| | 73 |

(b) Syphilis:

| | |
|---|---|
| Mentioned as positive | 7 |
| Mentioned as negative | 39 |
| Not mentioned | 27 |
| | 73 |

The above figures do not indicate that syphilis or the abuse of tobacco play any part in the causation of this condition. Of the other etiologic factors, mentioned generally as probable, such as exposure to cold, and alcohol, we have found no confirmatory evidence.

From the above statistics it can be seen that this obliterative disease of the vessels resulting in gangrene of the extremities, affects usually the legs, but occasionally also the arms. The possibility of a more general distribution of the condition seems never to have been suggested. That this may occur is conceivable. Our own case, and one which we have found in the literature, seem to bear out this idea. The latter reported by L. Renon[52], in 1905, is of such interest that we have thought it worth reviewing at some length.

The patient, a male aged 58, of good habits except for excessive smoking, had suffered from intermittent claudication and violent pain in the left foot for five years. During the seven months previous to admission the symptoms had become more marked, so that the patient's feet became cold and cyanotic on walking 200 yards. Four years before, he had had a slight paresis of the left arm, and a slight left facial paralysis. He complained of palpitation of the heart, and gave a history of typical attacks of angina pectoris. The heart and lungs were negative. The pulses of both feet were feeble. The left foot was swollen, cold, and cyanotic. The urine contained a trace of albumin, and no sugar.

Gangrene of the left foot appeared two weeks after admission, and a month later the patient died with delirium and coma. At autopsy the liver weighed 1550 gms., and was hard and cirrhotic. The kidneys showed old and recent infarcts. The spleen was large, hard, and strewn with infarcts. The heart was hypertrophied, its valves absolutely normal. The aorta was filled by a completely organized intimately adherent thrombus which, starting from a point just below the origin of the renal arteries, extended downwards into the iliacs and femorals. The femoral, popliteal, tibial, and dorsal vessels of the feet were obliterated by a similar thrombus. There was a large area of old softening in front of the right optic thalamus. Microscopic examination of the vessels showed organization of the thrombus, without change of the vessel walls, beyond a slight cellular infiltration.

A case reported by Hawkins[32] occurring in a girl of 11 years, and one by Bryant and Hale White[8] in a babe of six months, both instances of thrombosis of the vessels of the legs, with widely distributed visceral lesions, showed such marked arteriosclerotic changes that they cannot be considered as belonging to the class of cases under discussion. Several other cases which at first sight appear similar to that reported by Renon, are to be found, but in each one the presence of valvular disease, or of antemortem thrombi in the heart cavities, indicate the embolic origin of the condition. The absence of such was definitely stated in the above case, which, with the absence of involvement of the vessel wall, seems to point to a primary arterial thrombosis as the cause of the process. It is interesting to note that, although during life the condition was confined to the legs, after death lesions of the liver, spleen, kidneys, and brain were found. In the absence of a focus for embolism, is it not probable that the lesions of these organs were due to a thrombotic process in their vessels similar to that in the vessels of the legs?

The following case which came under our observation in the Lakeside Hospital and which owing to the kindness of Dr E. F. Cushing, we are enabled to report, presents many points of similarity to that reported by Renon.

G. M., male, American, 23 years old, carpenter, single, had had the ordinary diseases of childhood, and typhoid fever. He had been short of breath on exertion for three or four years. Eight months ago he had a urethritis, and a soft chancre. He denied syphilis. He had been a very heavy smoker and a moderate drinker. The present illness began three years ago when the toes of his left foot became painful and got "black and blue." This condition lasted almost a month when the pain disappeared and the toes regained their normal color. Since then he has had such attacks at intervals of about a month. The toes of the left foot have recently become black and are very painful. The patient has been increasingly short of breath on exertion. Physical examination showed the toes of the left foot all discolored. The great toe was dark brown, the fourth toe was absolutely black, the others ranging in color between the two extremes. The toes were very tender and colder than those of the right foot. There was no definite line of demarcation. Fairly well marked general glandular enlargement was present.

The heart was enlarged to left and right. The right border 5 cm. to the right of the midsternal line, the sounds were clear, regular, and forcible.

The radial pulses were equal, regular, and of good volume, and compressible with difficulty. The femoral pulses were much more easily compressed than the radial. Blood pressure in the radial artery 205 mm. of Hg. (Riva Rocci.) No pulse was palpable in the left dorsalis pedis artery.

The liver dulness extended from the sixth rib to 5 cm. below the costal margin in the midclavicular line. The edge was indistinctly felt. There was no pulsation. No change in reflexes or sensations was demonstrated. The eye grounds were not remarkable. The urine contained a heavy trace of albumin, and no casts. The leukocyte count was 27,000.

On the day after admission, the patient's temperature rose to 101° F. He became somewhat delirious, and showed signs of breaking compensation. Five days after admission, there was slight dulness with a few scattered patches of tubular breathing and a few fine moist râles at the left base behind. The temperature ranged between 101 and 103°, pulse between 100 and 120, the respirations were 30, the leukocyte count 31,000. Lumbar puncture was negative. Seven days after admission there was flatness and loud tubular breathing and increased fremitus at both bases, most marked on the left. The patient was somewhat delirious. Blood culture was negative.

Nine days after admission, the signs of consolidation still spreading and the respiration 50, the patient died.

At autopsy, the gangrene of the foot was as previously described. The heart was greatly hypertrophied and dilated, no sign of antemortem thrombi was present in any of the heart cavities. The valves were in no way remarkable. There was bloody fluid in both pleural cavities. The lungs showed massive hemorrhagic infarctions, the vessels leading to the infarcted areas filled with fresh red thrombi firmly adherent in places to the vessel wall. The liver was enlarged and pale. On the anterior aspect of the right lobe, the capsule was thickened and contracted. There was great increase of connective tissue throughout the right lobe. The spleen was much enlarged and hard. The capsule was thickened, and the connective tissue increased. Along the periphery were several old healed infarcts and throughout were numerous more recent areas of anemic infarction. The kidneys showed little gross change beyond fairly marked congestion. In the aorta at a point immediately below the origin of the renal artery was a mural thrombus 4.5 cm. in length. The thrombus completely surrounded the lumen of the aorta narrowing it to about one-half of its usual diameter, it was pinkish gray, firm, longitudinally striated, and firmly adherent to the vessel wall. On its surface were several small, fresh, red thrombi. The remainder of the aorta showed a slightly raised longitudinal, yellow streaking with occasional small, raised, white patches of intimal thickening. On the whole, however, the aorta varied little from the normal. The first portion and the arch of the aorta were free from change of any kind. Nothing resembling syphilitic aortitis was seen.

Microscopic examination:

Heart: The heart shows hypertrophy and marked fibrous myocarditis.

Lungs: The lungs show massive hemorrhagic infarction, evidently of recent origin. In many of the small veins and capillaries, which are everywhere widely dilated, can be seen what appear to be agglutination thrombi, formed of fused red blood cells. In what seems to be the beginning of this process, the staining reaction of the fused cells is unchanged, that is they stain straw colored with eosin and about the same tint as unchanged cells in the same and other vessels. These masses of fused red blood cells may fill three-fourths or four-fifths of the lumen of the vessel. In vessels so affected there may be a number of leukocytes, which rarely occur scattered, but are usually present in larger or smaller clumps. In what appears to be the next stage of the process, the lumina are completely blocked by masses of fused red blood cells containing a variable number of leukocytes. In these vessels, the plugs of fused cells stain deeply pink with eosin, either in whole or in part. This is in striking contrast to those previously described. These deeply staining masses may be smooth and glassy, but are more often granular in appearance. In some vessels of this class, that is the small veins and capillaries, fibrillated fibrin can be seen.

The larger branches of the pulmonary veins have their lumina completely plugged by solid masses, composed in large part apparently of fused red blood cells, but containing in addition rather dense strands of fibrin; in the fibrinous areas are numbers of leukocytes. In some of these pulmonary veins of medium size, typical mixed thrombi do occur. Can these be secondary thrombi, formed about emboli of agglutinated red blood cells, which have passed from the pulmonary capillaries into these veins? The blood in the alveoli surrounding the vessels plugged with agglutination thrombi shows no tendency to a similar agglutination, each cell preserving its integrity and individuality.

The small and medium sized arteries are plugged with typical mixed thrombi, in which red and white cells in varying proportion are entangled in the fibrin network. No sign of agglutination thrombi was seen in any of the arteries of the lungs. The walls of the small and medium sized arteries show nothing remarkable.

The main branch of the pulmonary artery is filled with a mixed thrombus adherent to the vessel wall at two or three points, elsewhere it has separated from the vessel by contraction; at the points where the thrombus is adherent, definite beginning organization can be made out.

The wall of this vessel shows slight degenerative changes. There is a definite proliferation of the subendothelial layer of the intima which tends to be of a somewhat nodose type, giving the lumen a slight irregularity of outline. These nodes of intimal proliferation correspond definitely to areas of connective tissue proliferation in the media. The changes in the media, however, are slight, both muscular and elastic elements being on the whole well preserved. The adventitia shows nothing remarkable.

Liver: The capsule shows in places a rather marked thickening with active cellular proliferation of connective tissue. Throughout the liver there is an increase in the perilobular connective tissue. Beneath the capsule for a distance of about two cm. this is very marked, while in the superficial two or three mm. it is intense, no trace of liver cells remaining. The new formed connective tissue is of a very cellular character. There is some new formation of bile ducts, but these are poorly differentiated. The branches of the portal veins in this area, both large and small, are completely obliterated by a richly cellular connective tissue, evidently the result of organization of thrombi. Some of these are canalized and one or two show complete hyaline degeneration. Some of the arteries in the affected superficial part of the liver show a slight intimal proliferation, but in the majority, the intima is unchanged; nearly all, however, show hypertrophy of the middle coat, with hyaline degeneration of that layer. The walls of the bile ducts are also thickened. The rest of the liver shows evidence of marked chronic passive congestion, with fairly widespread central focal necroses. No sign of recent or agglutinative thrombi in portal vein, liver capillaries, hepatic artery, or vein were seen.

Spleen: The spleen shows numerous infarcts of varying age, but none of them of very recent origin. The oldest are completely fibrous. The remainder of the spleen shows a moderate passive congestion.

The condition of the vessels is extremly interesting. Throughout the spleen, but especially in the healthy tissue near the margins of the infarcted areas, one finds many of the sinuses filled or partly filled with deeply pink staining granular masses, exactly similar to those described in the capillaries of the lungs. This material resembles fibrin closely in appearance and staining, but yet is distinct from it. These masses show no signs of fibrillation, and are of a glassy appearance, frequently on focussing one can make out what appear to be the shadows of agglutinated red blood cells. Sometimes a sinus can be seen partly filled by such an agglutination thrombus, while the remainder contains unaltered blood cells. Several sections through one of the medium sized veins were seen, containing a typical hyaline thrombus, almost certainly an older stage of a thrombus formed by agglutinated red blood cells. In places the endothelial lining of this vessel still remains, and at one point a space between the thrombus and vessel wall, lined by endothelium and filled with unaltered red blood cells. can be made out.

The capillaries and the small arteries show nothing remarkable, but in the medium and large arteries are most extensive changes. A few of these vessels appear normal, a few show a moderate degree of intimal proliferation with hyaline degeneration of their walls. The majority, however, especially in the neighborhood of the infarcted areas, show complete obliteration of their lumina by a dense connective tissue sometimes fibrous, sometimes richly cellular. In some the obturating mass shows beginning hyaline degeneration. Practically all these obliterated vessels contain one or more blood spaces, lined by endothelium and filled with blood. The vessels obliterated by more cellular tissue show in addition to such blood spaces numerous capillaries. The middle and outer walls of the vessels show little change. Sections stained for elastic tissue show the elastic laminae of the obliterated vessels heavy and wavy, nowhere do they show fibrillation or reduplication. In the obliterative tissue, a few fine fibrils of elastic tissue arranged circularly about the vessels can sometimes be made out but these are always very minute, never numerous, and are confined to the region immediately inside the internal elastic lamina. Altogether the appearance is very definitely that of organization of thrombus and not intimal proliferation.

Kidneys: The capsule varies, where the underlying tissue is normal, the capsule is of normal thickness. Over the greater part of the sections examined, however, the underlying parenchyma shows marked increase of fibrous tissue and here the capsule is greatly thickened. In such areas the tubules have almost entirely disappeared, those that remain are compressed and atrophic. The glomeruli also show marked changes, but as compared with the tubules, they are well preserved. Most of them show a thickening of Bowman's capsule, which in some is marked, while some are entirely replaced by connective tissue. This increase in connective tissue is definitely patchy in character, the patches being sharply marked off from the intervening tissue, which shows nothing pathological except a slight cloudy swelling of the convoluted tubules. The medulla shows a general increase in connective tissue. Hyaline casts are fairly numerous.

The vessels of the kidneys show very important changes. The capillaries of the tufts show nothing remarkable, but many of the intertubular capillaries show marked proliferation of their endothelium. Many of the small arterioles also show definite intimal proliferation, which in a few cases has led to complete obliteration. It is very noticeable that the intertubular capillaries and small arterioles, which show this intimal proliferation, are found only in the areas where the fibrous tissue is increased. Where the tissue is normal, there these vessels show no change.

The medium and large arteries, however, show by far the most marked changes. Some of them are normal, but about half the vessels of this size, in the sections examined, are filled by a cellular connective tissue, pierced in places by one or more spaces lined by endothelium and containing red blood cells. These vessels show the characteristic picture of organized thrombi. In one section can be seen such an artery, which unmagnified is about the size of a match. This vessel is completely filled by dense fibrous connective tissue, pierced in three places by small vascular channels. The vessel presents a thin outer fibrous coat containing numerous nuclei, a thick middle muscular coat, and a pale bluish staining central portion, consisting of dense fibrous tissue, in which are several capillaries and the three blood spaces mentioned above. These blood spaces are lined by endothelium, and surrounded by distinct walls of pink staining more regularly arranged fibers, showing a definite circular arrangement about the spaces. These are apparently canalized channels in an old organized thrombus. One of these canalized channels is in turn almost completely obliterated by a mass of cells, which appear endothelial in type, but are free from the lining cells, except at two points. The vasa vasorum, of which there are seven grouped about the vessel, are very large and thick walled, their lumina almost completely obliterated by what looks like proliferation of the intima.

Sections of this vessel stained with Unna's orcein, show very little elastic tissue in the media, but what there is, is normal in appearance and arrangement. The internal elastic lamina is heavy, it shows well marked reduplication and in places fibrillation. No elastic fibers can be seen in the obliterating tissue, except a few extremely minute twigs situated immediately inside the internal elastic lamina. The large and medium sized arteries which are not obliterated show no thickening of their walls or other signs of arteriosclerosis. In some of the obliterated vessels, the obliterating tissue has undergone hyaline degeneration. This is very well seen in a section of one of the large arteries, in which one of the canalized channels, has in turn undergone thrombosis, with subsequent transformation of the organized thrombus into hyaline. No sign of anything resembling agglutinative thrombi was seen in the kidney.

Vessels of the foot: No examination of the vessels of the leg could be made, as the relatives refused to allow any dissection of the extremities whatsoever. In sections through the skin of the foot near the area of gangrene, a great variety of changes are seen in the vessels. The largest, an artery the size of the dorsalis pedis, has its lumen almost completely obliterated by a canalized thrombus which has undergone hyaline degeneration. All three coats of the vessel show changes. The intima and media being both moderately thickened, while the adventitia is markedly so. The vessels a little smaller than this vary, some show no change, while others show well marked hypertrophy of the media with a marked thickening of the intima, resulting in a greatly reduced lumen of irregular outline. The small arterioles also vary, some are unaltered some show partial or complete obliteration of their lumina due apparently to intimal overgrowth, while many contain thrombi which have undergone hyaline degeneration.

Aorta: Sections through the mural thrombus in the aorta, show that it is formed by a loose connective tissue, the superficial layers of which show hyaline degeneration. The thrombus is covered by endothelium, except at some points. No elastic tissue fibrils can be seen in the thrombus. This organized thrombus is from two to three times the thickness of the aortic wall. The aortic wall beneath the thrombus shows little change. Sections stained with hematoxylin and eosin, Van Giesen's picrofuchsin stain and Unna's orcein show both muscular and elastic elements of usual appearance and arrangement, except in the outer fourth of the media. Here the ingrowth of capillaries from the adventitia has been accompanied by slight proliferation of cellular connective tissue. Sections through the aorta at other levels show an irregular thickening of the intima, corresponding to areas of degeneration in the inner third of the underlying media. This thickened intima contains very numerous, regularly arranged, new formed elastic fibrils, in marked contrast to the organized thrombus in which no trace of elastic tissue appears. The outer layers of the media show also a slight connective tissue proliferation.

The interpretation of the above findings presents some difficulties. It is unfortunate that we were unable to examine the vessels of the legs. The vessels in the skin, proximal to the gangrenous area, one of which was as large as the dorsalis pedis show, however, definite thrombosis, and it is probable that the process in the femoral and tibials was a similar one. The kidneys are extremely interesting. At first sight the narrowing of the lumina of the small arteries and capillaries would seem to point to an arteriosclerotic process. On the other hand the distribution of the areas of fibrosis and their sharp demarcation, and the fact that the vessels in the unaffected tissue show no change whatsoever, is against this view. May not these small vessels be terminal branches of the larger trunks which were seen filled with organized thrombi? Through the canalized channels in such vessels only a small amount of blood could flow, and the proliferation of the intima in these terminal branches may be simply a physiological narrowing of the lumen to compensate for this lessened flow. If such is the case, the whole process would appear to be due primarily to thrombosis of the larger arteries. The occurrence of intimal proliferation in some of the vessels of the foot can be similarly explained. In the spleen we have also thrombosis of the large and medium sized arteries leading to extensive infarction. The cirrhosis of the liver occurring both in this case and in that reported by Renon is somewhat puzzling. At first we were inclined to consider it either syphilitic or due to prolonged extreme passive congestion. The absence of gummata, however, and the occurrence of definite organized thrombi in the branches of the portal vein, in the affected area, seems to indicate that the process here is also one of thrombosis. In the pulmonary artery we have definite thrombi showing beginning organization resulting in massive hemorrhagic infarction of the lungs. It seems highly probable that this is simply the early stage of the process occurring in the liver, spleen, kidneys, legs and aorta. It is well known that all the stages of thrombosis and organization may be found in the vessels of the leg of one individual. Why may we not find, then, different stages in the various organs of one individual?

The possibility of embolism must of course be considered. That the thrombosis in the vessels of the legs may be due to an embolus from the thrombus in the aorta cannot be denied. The situation of the thrombus below the origin of the superior mesenteric and renal vessels seems, however, to exclude the probability of embolism in liver, spleen and kidneys. In the case of the pulmonary artery it is hard to imagine such an origin for an embolus. As the foramen ovale was closed, retrograde embolism is excluded. Many cases showing lesions similar in the gross to this case have been reported, but in these the presence of valvular disease or antemortem thrombi in the ventricles, both entirely absent in our case, gave a definite focus for embolism.

The significance of the occurrence of agglutination thrombi in the spleen and lungs is difficult to estimate. Their occurrence in the lungs alone, would not be of much significance for it is well known that one of the most common sites of such thrombi is in hemorrhagic infarcts. The finding however of similar thrombi in the spleen in tissue outside the areas of infarction, and of hyaline thrombi in one of the veins of that organ, suggests that their occurrence may be of more significance. In this connection the liver is also of interest.

Mallory[43] has shown that the focal necroses of the liver in typhoid fever are due to thrombi formed by and around endothelial cells. Boxmeyer[5] has shown that the focal necroses of the liver in experimental hog cholera, are due in part to similar endothelial cell thrombi, but also to agglutination thrombi in the portal veins and liver capillaries, especially the former. He has pointed out moreover that the areas of necrosis are usually about the periphery of the lobule and that it is the superficial portion of the liver which is chiefly affected. Pearce[50] and Flexner[23] have produced similar lesions by the intravenous injection of hemagglutinins.

In the case reported here, we have focal necroses of the liver of central situation. These are unquestionably entirely due to the chronic passive congestion, which is marked in this case. But in addition we have, in a patient suffering from multiple thrombosis and in whom agglutinative thrombi were found in the lungs and spleen, a marked perilobular formation of connective tissue, affecting chiefly the superficial layer of the liver. In the absence of any known cause for such a cirrhosis, may not this be simply the result of a previous extensive necrosis, due to thrombosis in the portal circulation, possibly agglutinative in origin?

The fact that in the spleen and kidneys it is the large arteries which show the most extensive change, while the small arteries appear to be only secondarily affected, is of course strongly against the probability of the whole process being agglutinative in origin.

We believe then that we are dealing here with a case of general arterial thrombosis, exactly similar to that found in the extremities in the condition known as spontaneous gangrene.

As regards the etiology of this condition, we must admit that like all previous observers, we are still completely in the dark. Syphilis, alcohol, and exposure to cold have all been tried and found wanting. In the cases studied by us, we have found no evidence of the abuse of tobacco as an etiologic factor, but recently Erb[20], from the study of a large number of cases of intermittent claudication, undoubtedly a closely allied condition, has laid stress on the importance of the abuse of tobacco in that condition.

In closing we should like to call attention to the possibility of agglutination bearing some part in the origin of this process. It is interesting to note that as long ago as 1883 von Recklinghausen[31] mentioned the possibility of such an origin. The finding of agglutinative thrombi in the spleen and lungs in the case reported here suggests that a study of the hemagglutinins in cases of spontaneous gangrene, might possibly throw some light on the nature of a process at present enshrouded in darkness.

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No. 5

# ANOMALOUS SCARLET FEVER

## A REPORT OF THREE EPIDEMICS *

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During the past decade there have occurred in Lakeside Hospital three epidemics of what is thought to be anomalous scarlet fever. In each of these epidemics the disease might have passed unrecognized, or at least some doubt might have been entertained as to its nature, had not one or more typical cases occurred which acted as a diagnostic control. These epidemics were characterized by the mildness of the attack, the benign course of the disease together with the suppression or complete absence of the exanthem together with some other of the more important symptoms.

The first epidemic occurred in the winter of 1904-5 and started in the children's ward, but before strict quarantine and disinfection terminated its spread, the medical and surgical wards likewise contributed until eighteen cases were observed.

### REPORTS OF CASES

Case 1.—A child admitted with some slight ailment was observed to have a faint rash on the neck and face which soon disappeared, although a redness of the fauces persisted somewhat longer. There had been but a slight rise in temperature and the case attracted no special attention.

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* Read in the Section on Dermatology of the American Medical Association, at the Sixty-first Annual Session, held at St. Louis, June, 1910.

Case 2.—A child, aged 3, was admitted to the surgical service with tuberculosis of the knee. On November 30, the knee was aspirated and iodoform emulsion was injected. December 1, the temperature, which had been about normal, registered 103 F.; it became normal again on the 2d, and the following day again arose to 103. On the 4th, a slight reddish, papular rash noticed over the trunk, with flushing of the face. This was thought to be due to iodoform poisoning. Further examination, however, brought to light changes in the fauces; and the tonsils were red and slightly swollen. Three days later, December 7, the night nurse on duty in this ward came down with a typical infection of scarlet fever of moderate severity, whereon both were immediately isolated. The child ran a mild course with slight desquamation and was discharged Jan. 13, 1905.

Case 3.—The case of the nurse above mentioned ran a typical course of moderate severity. It is noted that differential blood-count showed a marked increase in eosinophils.

Case 4.—A child, aged 11 months, was in the surgical service for a hare-lip operation. Some time after the operation it was noticed that the temperature, which had been normal, suddenly arose to 103, but returned again to the normal two days later. Three days after this, December 4, it registered 101, and the next day the face was flushed, except around the mouth, and a slight rash could be made out over the body. There was also inflammation of the throat. The child was isolated, and three days later the rash had disappeared. The temperature at this time was 99. Desquamation had already begun around the neck. From this time the temperature became irregular and later a discharge was noticed from the left ear. The notes of the case show that the child was discharged well, Jan. 11, 1905.

Case 5.—A hospital nurse, aged 19, complained of a headache, was chilly with a sore throat on December 4. On the afternoon of the same day the left tonsil was red and puffy, with pin-point white spots. The temperature was 101.6. The next morning she still had headache and vomited once after taking magnesium sulphate. The tonsil being still "puffy and sore," the patient was taken to the operating-room to have it incised, when one of us was asked to see the case. A diagnosis of scarlet fever was made and the patient isolated. Previous to this no rash had been seen, although a slight itchiness of the skin had been complained of. At the time of our examination, however, a pinkish velvety rash could be made out on the sides of the neck and upper part of the chest. The face was deeply flushed, except about the mouth. The following day the rash was well out and of typical appearance. It then became patchy and began to fade two days later. Both tonsils became covered with a grayish exudate and general glandular enlargement was present. Throat cultures showed the staphylococcus and streptococcus. Blood count on December 4 showed eosinophilia 8 per cent.; no other change noted. The case thenceforth ran an uneventful course.

CASE 6.—A hospital nurse, aged 29, on December 8, complained of chills, sore throat, headache and vomiting. These, however, were not very severe, and she continued on duty. Her appetite seemed unimpaired. Two days later the face, shoulders and outer aspect of arms were found to be flushed. The tonsils were slightly enlarged and injected and the tongue coated. The following day the erythema had assumed a blotchy appearance and was limited to the regions first involved. It did not extend and was followed by a slight branny desquamation on the arms and face. During the whole course the temperature did not go above 99.

CASE 7.—A child, aged 4, was admitted to the hospital December 6 suffering from acute bronchitis; while in the ward the temperature ran from 99 to 100. On December 21, the child had a slight erythema on the trunk, legs and face and the tonsils were red and swollen. The next morning the rash was faint, the tongue was coated and the tonsils were very large. By the 25th the rash had disappeared; although the patient was under close observation no appreciable desquamation followed. The urine showed a faint trace of albumin from December 12 to December 24. The temperature was never above 100.

CASE 8.—The patient, a child aged 3, on surgical service was operated on for club-foot on December 6, and on the 7th the temperature arose to 100.5 and remained between that point and normal until December 14. On that day, although the patient had not formerly complained, the temperature arose to 102.5 and there was a slight reddish punctate eruption over the body, with the face flushed, excepting the circumoral region. The tongue later presented a strawberry appearance and the tonsils were large and red. There was a general glandular enlargement. On the 20th, desquamation began and the child was discharged well one month later.

CASE 9.—A nurse, on duty in the infected ward, had scarlatina accompanied by arthritis, which was not severe. Her case ran a typical course. The patient made an uneventful recovery.

CASE 10.—A laborer, aged 30, was admitted to the surgical service for a herniotomy. On December 20, four days after admission, there was a slight rash on the body, with an injected throat and large, red tonsils. The tongue was swollen and coated, glands enlarged. On January 1, desquamation started and patient was discharged January 16. At no time was the temperature above normal, excepting on December 29, when the wound became infected and the temperature remained above normal for a few days. The leukocyte count was 23,000, eosinophiles 11 per cent., blood-cultures negative.

Case 11.—A miner, aged 28, had been admitted to the hospital on September 4 for paraffin injection of the nose. On December 22, the patient had swollen tonsils, a suggestive tongue and a very slight, pinkish, macular rash on the body, the macules being from ⅛ to ½ inch in diameter, with a slight erythema between them and looking somewhat like measles. There was on exanthem on the buccal mucosa, no nausea, sore throat or fever; but the patient had some headache and general glandular enlargement. On December 21, there was a slight desquamation on the right hip, which lasted only a few days; no desquamation was noticed elsewhere. The urine showed a faint trace of albumin from December 23 to January 10; the temperature was never above 99.

Case 12.—The patient, a nurse aged 20, on December 14, had some headache, sore throat and felt feverish, vomiting four times. On examination there was a slight erythema of the arms, over the region of the scapulæ and on the face, except the circumoral region. The patient also had a coated tongue and swollen, red tonsils covered with a slight exudate. The glands were not enlarged. By the 20th, the rash on face and arms had faded, having appeared nowhere else, and on December 28, there was a very slight desquamation present on the areas involved. The nurse was discharged January 9, having never had a temperature above 100, and that only during the first night. The urine showed a faint trace of albumin up to January 6.

Case 13.—A nurse, aged 23, on December 15, had headache, sore throat, and felt chilly and feverish. The next day there was a slight rash on the chest and neck, with a temperature of 100.5. The tongue was swollen and coated, and the tonsils red and enlarged. The glands about the neck showed enlargement. By the 20th the rash had disappeared, but no desquamation followed. On the 24th the throat again became sore and the glands enlarged and tender, with a rash over the whole body. Then typical desquamation appeared, and the patient was discharged January 10. Except during the first night the temperature was never above 100. The urine showed a faint trace of albumin for a few days.

Case 14.—A maid employed in the hospital, aged 25, on December 22, had a sore throat, headache, backache and was nauseated. She continued to work until two days later, when on examination she showed a flushed face, except the circumoral region, with erythema over the chest and shoulders. The tongue was large and coated, papillæ prominent, tonsils red and swollen and glands generally enlarged. The erythema was entirely gone by December 27, but the patient never had the slightest trace of desquamation. The urine showed a faint trace of albumin from December 25 to 29. There were no casts. The leukocyte count was 13,600, eosinophiles 13 per cent., throat cultures gave staphylococci and streptococci. The temperature was never above 99, nor was the pulse over 100.

The remaining cases in this epidemic showed nothing unusual except that they were very mild and comparatively of short duration. The points mainly to be noted in this epidemic are the following:

1. The relatively large numbers of adults, chiefly nurses in the infected wards. Of eighteen attacked, eight were adults, six were nurses or otherwise employed in the wards, and two were adult patients exposed while in the wards.

2. The benign character of the infection and its short course (average being 3.9 weeks from appearances of rash to end of desquamation). The only constant symptoms that could be regarded as at all typical were the onset and the congestion of the fauces. The cutaneous manifestations, with two exceptions, are evanescent and alone insufficient for the purpose of diagnosis.

The second epidemic began in April, 1907; there were eleven cases reported, although the case notes were found even less complete than in the first epidemic. As nearly as can be ascertained the epidemic began in the children's ward as an indefinite sore throat with no distinct or constant cutaneous manifestations.

Convalescence, however, was more protracted than was observed in the first epidemic and even a larger proportion of adults were attacked. The following may be taken as the most typical examples of this epidemic:

Case 15.—A nurse, aged 20, was admitted to the isolation pavilion April 19, 1907, after having had a slight sore throat, headache and malaise since April 16. On examination there was a faint rash over the entire body, general glandular enlargement, tongue negative, tonsils injected and the right one enlarged. There was nothing abnormal in the heart or lungs. The rash disappeared by April 22, and desquamation, which was never very profuse, did not start until May 1, and lasting until July. The temperature was never above 99.5, excepting at one time, when it went up to 100.3. The pulse was never more than 110; urine was negative. The patient was discharged July 1, 1907.

CASE 16.—A nurse, aged 21, on July 13, complained of sore throat, weakness, nausea, cold perspiration and fever. The next day she noticed an eruption and on examination there was found a marked erythema with edema of the face. There was a strawberry tongue, throat swollen, tonsils covered with a membrane, glands all palpable. The cutaneous rash and the membrane in the throat were gone by May 18 and desquamation started, lasting until July. The temperature on admittance was 104 and pulse 120, both of which came down to normal in four days. No complications were noted, excepting a slight trace of albumin in the urine. Cultures of the streptococcus were obtained from the throat.

CASE 17.—A nurse, aged 20, with previous history of rheumatism and chorea, had been on duty in the infected ward. On May 9 she complained of weakness, sore throat and malaise. On the 10th a rash was noted on the chest, arms and neck, and on examination there was a faint erythema over the entire body, with a strawberry tongue, swollen tonsils covered with a heavy membrane and general glandular enlargement. The throat swab showed only streptococcus. The rash was gone by the 13th, and desquamation began about a week later, being finished by July. The patient developed a slight arthritis and myocarditis. The temperature remained about 101 until the 15th. The urine showed a faint trace of albumin.

CASE 18.—A nurse, aged 19, awoke on May 9 with a slight sore throat, nausea, malaise and slight fever. The next day a rash was noticed, and on examination the patient had a very slight erythema over the entire body, with a negative tongue and injected throat and tonsils. The superficial glands were slightly enlarged. Desquamation began on the 25th, lasting until July, although never very extensive. The urine showed a faint trace of albumin; there were never any casts. The temperature was 100 on the first day, after that normal.

CASE 19.—A nurse, aged 20, on May 4, complained of severe sore throat, nausea and malaise. Early in the afternoon an eruption first appeared on chest and neck. The following day a general marked erythema was present, with glandular enlargement, tongue large, swollen, reddened, and throat greatly congested. The rash had disappeared on the 19th, and the throat was normal by the 21st. Desquamation began June 1 and lasted until July 17, although never very profuse. The temperature on admission was 102, but soon fell to normal, where it remained. The urine showed a faint trace of albumin.

In this epidemic, as in the one preceding, there developed no serious complications or fatal results. The features to be noted are the sudden onset with marked involvement of the fauces and comparatively high temperature followed by a varying degree of the exanthem. There was a rapid subsidence of all symptoms followed by a retarded but protracted period of desquamation.

What may be termed the third epidemic occurred in 1909. Although but three cases were observed they furnished features that are thought worthy of mention.

Case 20.—A child, aged 9 months, was on the surgical service for cervical adenitis, being admitted Oct. 31, 1909. It had some discharging sinuses, which were being packed with iodoform gauze, and on March 21 the child developed a slight scarlatiniform rash, with a temperature of 100. The rash was faint, atypical, lasting only three days. There was no nausea or vomiting. The throat was congested and reddened, while the tonsils were enlarged. At first the case was regarded as an iodoform rash, but as the patient had 7 per cent. of eosinophiles in a differential count of 200 cells she was isolated, and while in isolation had a typical desquamation and double otitis. The urine also had a faint trace of albumin. The temperature never went above 100 until the otitis developed.

Case 21.—The child in the next bed to the patient last described came down three days later with a typical scarlet fever. She was a girl, aged 3, in the hospital for acute anterior poliomyelitis. The rash was marked and typical, with a temperature of 103, rapid pulse, vomiting, severe sore throat and a considerable enlargement of the tonsils. Two days later the rash faded and the case ran a typical course of desquamation, with eventually a complete recovery.

Case 22.—A nurse, aged 24, was nursing the child with obscure so-called iodoform rash. Two days later she was taken off duty because of a sore throat and a feeling of malaise and headache. The throat was very red and edematous, the tonsils greatly swollen, so that they met in the median line. They were partially covered with a membrane, but showing no diphtheria bacilli. The glands were not enlarged, except those of the neck. The temperature was 100 on admittance, 103 two days later and afterward never above 100. On December 1 the patient vomited several times, but the tongue was never typical. The leukocyte count was 19,000; differential showed no eosinophilia; urine was negative. The patient never showed any rash or desquamation, but considering her symptoms it was deemed justifiable to place her in this list.

## CHARACTERISTIC FEATURES

The most striking characteristics in this series of 32 cases occurring in three epidemics were the following:

1. *Erythema.*—There were three cases in which erythema was very slight; in one it was absent and in one it was confined to small areas and very evanescent. Two of the patients with slight erythema had it confined to the neck, shoulders and arms. It may be well to mention, in passing, that one patient had a secondary erythema.

2. *Temperature.*—This varied from normal to 105 F. Four patients never had a temperature above 99, two never above 100, and the remainder ran between 100 and 105, most of them, however, between 100 and 102.

3. *Desquamation.*—There were six cases in which the desquamation was typical and one in which it was faint but general. One patient never showed any desquamation except around the neck; another none except on the right hip. There were two in whom it was confined to the face, arms and shoulders, and three never showed any desquamation.

4. *Urine.*—In only two cases was there absence of all signs of nephritis, while all the others had a faint trace of albumin; and in one case there were casts. Two of the three patients showing no desquamation had a faint trace of albumin for a few days.

5. *Angina.*—Practically every patient in this series had a severe angina, seven of them also showing presence, more or less, of a membrane in the throat.

6. *Blood.*—The only changes noted were a marked increase in the number of leukocytes in a few cases, and in a number of instances the differential blood-count

showed a high percentage of eosinophiles, which is in accord with the observations of Van den Berg[1] and Kotschetkoff.[2]

### LITERATURE OF THE SUBJECT

In the literature dealing with this special phase of scarlet fever, namely, the absence of exanthem with little or no rise of temperature together with other manifestations characteristic of a faint type of the disease, we find as far back as 1839, Taupin[3] observed, during the course of his internship at the Hôpital des Enfants Malades, an epidemic of five cases of scarlet fever, in two of which there was no eruption. The year previously Eiselt[4] published an account of a severe case of scarlet fever in a girl of 20, in which there was no eruption, although the girl had a marked desquamation associated with anasarca. She eventually recovered.

Buttura[5] in 1857, was called on July 10, 1856, to see a young man who suffered from a well-marked scarlatinous angina. The eruption was copious and the disease followed a course typical of scarlet fever. Four days later a little girl in the same family developed croup; angina marked but no eruption throughout the course of the disease. Five days later, on June 20, a little brother also developed intense characteristic anginous symptoms; the odor from the mouth was pronounced. No eruption could be observed at any time. Convalescence was prompt in all three. There were no sequelæ.

Buttura then enters into a discussion concerning the opinions of authors in regard to the possibility of scarlatina without eruption, and reviewed the literature of this subject at some length. He states that in September, 1829, there reigned in the village of Seine-et-Oise an epidemic of so-called common angina. Careful study by the local physician led to a diagnosis of scarlet fever with predominant mouth (throat) symptoms. In the Château de Villeroy, inhabited by Comte Friant and his family, thirteen persons were affected, and of these, five presented a special angina without eruption.

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[1] Van den Berg, J. B.: Arch. f. Kinderh., 1898, xxv, 321.

[2] Cabot, R. C.: Clinical Examination of the Blood, New York, 1897, p. 177.

[3] Taupin, Charles: Essai sur la scarlatine sans exanthème, Thèse, Paris, 1839; abstr. in Jour. conn. méd.-chir., vii, 151-155.

[4] Eiselt, J. N.: Fall einer Febris scarlatinosa sine Exanthemate, Med. Jahrb. d. k. k. oesterr. Staates, Wien, 1838, New Series, xv, 212.

[5] Buttura, C. A.: Des fièvres éruptives sans éruption et particulièrement de la scarlatine sans exanthème, 1857, Paris.

Trousseau observed scarlatinous angina without eruption of the skin in 1828, at Cour-Cheverny. The diagnosis was made on the strength that a boy had distinct scarlet fever with eruption. Three sisters of the boy developed fever, angina, but no eruption.

He states that Dr. Carrière observed during an epidemic at Saint-Dié (Vosges), during the winter of 1842-1843, 34 cases of scarlet fever with an eruption in 23 only, and in the majority of these it was very slight. The disease ran a benign course. In one case of scarlatinous edema with albumin in the urine no sign of eruption appeared, although all the other symptoms of scarlet fever with angina were present.

Bouché (of Vitray) reported four cases of scarlet fever as follows: The first was typical scarlet fever without eruption; the next a typical case with eruption; the third was again without an eruption and the fourth again a usual case. Two of the cases were without eruption. The diagnosis was made from general symptoms and the presence of eruption in the other two cases occurring in the same house.

Legroux reported a case of scarlet fever in a chlorotic woman in whom the eruption could barely be made out. The eruption was likewise scarcely perceptible in an infant of four days who is supposed to have contracted it from the mother, who had scarlet fever on the second day of puerperium. The father had an angina without fever or redness of the skin at the time that the scarlet fever terminated in the mother.

In another house a boy had ordinary scarlatina; the sister developed a marked angina, with pronounced scarlet eruption and died. During the course of this affection the mother, her infant and a young woman of 24 contracted angina with pseudomembranous plaques, with fever, but without eruption, lasting six days. Three days after the death of the child the grandmother and the father presented guttural angina, slight fever, characterized by a bright redness, but no swelling.

During the epidemic in Berlin Dr. Helft observed cases in which no eruption appeared although all the other symptoms prevailed, occurring in families in which scarlet fever was present.

In an epidemic of scarlet fever at Loudon (Vienne), from March to September, 1841, Mondière reported that in one case of very severe angina the eruption was confined to the feet and hands only. In other cases no eruption appeared.

During the epidemic at Loches, 1835, Renaud observed three cases of scarlet fever in one family. Two children developed typical cases of the disease when the third one was stricken with all the severe symptoms that the others had shown, but at no time during the attack did it develop the slightest sign of an eruption. The course of the disease was quite severe in this case, but the child recovered.

Berrand further states that Krauss of Tübingen reports having observed scarlet fever without eruption in the proportions of 1 in 3. The cerebral symptoms predominated in these cases. He states that Dr. Maclintock reported three cases as follows: Child was taken with vomiting; condition did not improve; coma alternating with spasms, death ensued. On the day this child was buried another in the family was taken in the same manner; developed the same symptoms; marked convulsions and death. The third child was also taken. It, however, developed a typical scarlatina rash. No doubt the other two children died from scarlatina without exanthemata.

About the time Buttura's article appeared Bauer[6] reported an epidemic of 20 cases, among them being that of a boy who had, he thought, a very severe scarlatina, yet developed no observable eruption at any time. The patient eventually recovered after having had a post-scarlatinal arthritis.

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[6] Bauer, F.: Beitrag zum anomalen Verlauf des Scharlachfiebers, Ztschr. f. med. Chir. u. Geburtsh., 1859, xiii, 97.

Anderson,[7] Banks,[8] Whelan,[9] Robinson,[10] Dreyfus,[11] and Brissoe and Wetherill,[12] also reported similar cases about this time, all agreeing that in their experience scarlatina at times existed with absence or sparseness of the eruption as well as other symptoms of scarlatina. At such times it is impossible to make a diagnosis were it not for the fact that an epidemic of scarlet fever is in progress.

Furthermore Gosebler[13] in 1881 made a diagnosis of scarlatina in two children aged 30 months and 6 years respectively, despite the fact that they had no eruption, desquamation or throat symptoms. He based his diagnosis on the following grounds: that the children were ill for some time, the illness in each case being with fever and repeated vomiting, followed later by large amounts of albumin in the urine; and that it was at a time when scarlet fever was very prevalent in the town and quite fatal. Furthermore several cases of scarlatina without exanthemata had been observed. In 1892 Baiss[14] reported three cases in one family with the following history: The first child was found to have a temperature of 102; the next day the temperature was normal, but the child had a slight sore throat and some enlargement of the glands of the neck; otherwise it seemed to be well. There was desquamation later, however, and a few days after the beginning of the child's illness a second child was seized with more severe symptoms, and with an eruption which resembled measles. At this time the third child became ill with a typical scarlatinal eruption accompanied by jaundice. Were it not for the last case it would have been difficult to diagnose correctly those preceding.

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[7] Anderson, W. J.: Some Anomalous Cases of Scarlatina, Lancet, London, 1854, i, 327.

[8] Banks, J. T.: Dublin Hosp. Gaz., Anomalous Scarlatina, 1858, New Series, v, 65.

[9] Whelan, J. H.: Modified and Anomalous Scarlatina, Lancet, London, 1883, ii, 769.

[10] Robinson, C. H.: Scarlatina sine Eruptione, Lancet, London, 1870, i, 227.

[11] Dreyfus, Brisac: De la scarlatine anormale, à propos de trois cas observés dans la même famille, Gaz. hebd. de mèd., 1884, Series 2, xxi, 606.

[12] Wetherill, Horace G.: A Series of Unusual Cases of Scarlet Fever, Tr. Med. Soc., New Jersey, 1888, p. 225.

[13] Gosebler, A.: Kurzer Bericht über drei Fälle von anomalen Verlaufe der Scarlatina, Prag. med. Wchnschr., 1881, vi, 385.

[14] Baiss, J. R.: Some Anomalous Cases of Scarlet Fever, Boston Med. and Surg. Jour., 1892, cxxii, 630.

Lee[15] reports sixteen cases, occurring in four families in which four adults and twelve children inhabited the same building. The series is noteworthy because of the absence of the exanthem as well as some other symptoms. In the first two only was any rash observed. The first patient when seen had a fast pulse, temperature 101, strawberry tongue, characteristic rash and sore throat. In five patients the glands were neither swollen nor tender. Only three had sore throat and only two vomited. The temperature in all ranged from 101 to 102; the pulse in the children, from 140 to 148, and in adults from 130 to 134. The following sequelæ were noticed: One patient developed diarrhea, two bronchitis, and in two only was there desquamation. In two after some exposure there followed swelling of the submaxillary glands with rise of temperature and accelerated pulse. One woman, contracting the so-called scarlatina five days after labor, had puerperal fever.

Warry[16] reported an interesting epidemic of 150 cases of scarlatina with sore throat but with an absence of rash. The entire epidemic both in regard to those having rash and those without rash were found to be due to the milk supply. The author believed the cases without an exanthem to be scarlatina for the following reasons:

1. Many of the patients had desquamation during convalescence.
2. Others had kidney complications.
3. Several had arthritis.
4. Several developed otitis.

Further, it may be interesting to note that scarlatina without fever has also been recognized not infrequently and corresponds more or less with some of our cases.

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[15] Lee, W. R.: Med. News, Philadelphia, 1892, p. 186, Scarlatina sine Exanthemata.

[16] Warry, J. K.: Special Report on a Recent Outbreak of Scarlatina and Sore Throat Disease in Upper Clapton, Practitioner, London, 1892, xlix, 63.

D'Amore[17] reports several cases and Brunard in the past year states that he has observed a number of cases about Brussels. He mentions in particular three cases, in children, which occurred in one family. They ran an afebrile course and were mild, yet all three had typical scarlatina complications.

McClanahan[18] at Woodhull, Ill., also had the opportunity of studying afebrile scarlatina in a series of 150 cases. Many of his cases also were notable on account of the absence or mildness of the exanthem and other symptoms.

He says that in December, 1892, he was called to see a patient with a temperature of 101, pulse 100, restless and complaining of itching. She had red faucial and buccal membranes; the tonsils had a fibrinous deposit over them, no strawberry tongue. By the next day restlessness had disappeared but there was a typical scarlet fever eruption although the temperature and pulse were normal. In another twenty-four hours the throat was clear, the rash and all other evidences of scarlatina had disappeared and the patient had no further trouble.

From this time until 1893 he saw about 150 cases. The fauces were involved in every case, as was the presence of the strawberry tongue. In about one-third of the cases there was no eruption. In six of them it resembled that of rubeola and in three the surface was nearly scarlet, red, smooth and glossy but without the minute points seen in the scarlatina rash. In the remainder the exanthem was the ordinary scarlet fever rash except that its stages were of shorter duration.

Twenty of the cases were followed by otitis; this occurred irrespectively of the other symptoms. The temperature seldom rose above 102, and this fever rarely lasted longer than three days; in fact, in the majority, the temperature was normal by the third day. At times the disease appeared to be contagious, at other times not.

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[17] D'Amore, L.: Scarlatina apiretica, contribuzione alla casuistica, Progresso med., Naples, 1895, ix, 25.

[18] McClanahan, W. S.: Some Peculiarities in a Mild Epidemic of Scarlet Fever, Peoria Med. Jour., 1896, i, 339.

Rodger y Piza[19] had the opportunity of observing an interesting case. In a certain family there was a child who ran through a typical course of scarlatina. Rodger y Piza was suddenly called in to see a younger child who had had a high fever for twenty-four hours and was voiding dark urine. The latter on examination was found to contain blood, epithelial cells, casts and much albumin. The hematuria lasted for thirty days. On the twelfth to the fourteenth days there occurred a slight furfuraceous desquamation on the face and upper part of the chest and forearms. From the presence of scarlet fever in the house Rodger y Piza had not the slightest doubt that this was a case of scarlatina *fruste*, so called by Trousseau, only one symptom of scarlet fever being present.

## THE VARIATIONS OF SCARLET FEVER

From the foregoing it seems evident that what is known as scarlet fever varies greatly in its clinical manifestations. In a violent form it may cause death within a few hours, or in its mildest form it may be evanescent and difficult to recognize. As to the *materies morbi* which gives rise to scarlet fever we know nothing positively, nor of its mode of invasion. From the epidemics herein reported as well as others cited it would appear that the toxin varies in different outbreaks. From our observation it does not appear that mild infections beget malignant strains, or the reverse. Furthermore it should be remembered that in epidemics of a severe type atypical cases occur as frequently as in those of mild type.

From the fact that the tonsils are involved at a very early stage, and from the constancy with which this symptom has been noted, it would seem that the infecting agent gains access through these glands, as claimed by Dawson[20] and Lemoine.[21]

It seems unwise, therefore, with our imperfect knowledge concerning the etiology of scarlet fever, to regard these aberrant forms, which point strongly to some aberration of the exciting cause, as distinct affections. In 1894 Duke[22] endeavored to establish a "fourth disease" in the infectious exanthemata, but the consensus of opinion does not substantiate this claim. Our observations show that the most constant symptoms are the angina and slight nephritis, while an increase of eosinophiles in the blood was observed in a considerable number of our cases. Other phenomena are usually present even in atypical forms of the disease, but they are inconstant and subject to wide variation.

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[19] Rodger y Piza, Ramon: Un caso de escarlatina frustada, Rev. balear. de cien. med., Palma de Mallorca, 1903, xxiv, 27.

[20] Dawson, W.: Med. Chron., Manchester, 1893-4, xix, 217.

[21] Lemoine, G. H.: Bull. et mém. Soc. méd. d. Hôp. de Paris, 1895 and 1896; Gaz. Hôp. de Paris, Nov. 25, 1895, p. 1337.

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[22] Duke, Clement: Lancet, London, 1894, i, 791.

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No. 6.

# PELLAGRA IN OHIO: WITH REPORT OF A CASE.*

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UNTIL quite recently pellagra has been regarded as a disease limited to certain countries, mainly Italy, Spain, southern Austria and the Roumanian district, together with Egypt. Isolated cases, it is true, have found their way into this country, but not in sufficient numbers to obtain general recognition, nor to menace the health of its inhabitants. It is natural, therefore, that the report of a large number of cases of this disease occurring in this country should be received with some incredulity. Through the medical press physicians were aroused as to the possibility of pellagra existing in their several communities, and the lay press was not slow in publishing exaggerated reports and wild rumors concerning its magnitude. Naturally with this general awakening many suspected cases proved on examination to be ordinary affections. The following may be given as an example of some of these cases:

W. K., male, aged sixty-four, American, a marine engineer until two years ago when he took up the occupation of farming. About a year before the patient came under observation, in November, 1909, he developed a severe dermatitis on the dorsal surfaces of the hands, lower half of the forearms and face, which resisted the various forms of treatment employed (Figs. 1 and 2). The patient attributed the disease to the effect of ''corn smut'' with which he had come intimately in contact in husking corn the day preceding the outbreak. He further said that on account of the warm weather he had perspired freely and that the ''corn smut'' which was abundant was thus intimately brought in contact with the skin. The case was admitted into Lakeside Hospital as eczema. While in the hospital the eruption extended over the whole cutaneous surface, the palms and

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The patient was discharged from the hospital April 10, 1906, having remained only thirteen days.

She was again admitted May 11, 1906, complaining of increaseing dizziness, and was discharged June 2, 1906. During this time the sputum was repeatedly examined for tuberculosis with a negative result.

The patient was admitted the third time on October 27, 1909. Notes of her condition since last discharged show that she has had headaches almost constantly during the past year. The appetite has been poor, the digestion bad, and the bowels constipated. She has been vomiting intermittently for three or four days each week during the past three or four years. She often vomits before breakfast, also after meals. There is no pain, but a heavy feeling which is relieved by vomiting. There has been no hæmorrhage.

Physical Examination. The nutrition is very poor. There is marked emaciation. The muscular system is markedly atrophied.

The Skin and Mucous Membrances show some anæmia. There is no œdema, cyanosis nor icterus. The skin is white, harsh, dry, and scaly. There are white pigmented spots in the mouth under the tongue. There is brown symmetrical pigmentation on the dorsal surface of both hands.

The Glands are all palpable except the epitrochlears.

Eyes. The pupils are small, equal, round; react sluggishly to to light and accommodation.

The Tongue is moist and protrudes with tremor toward the left side.

In the Lungs the note is shorter and duller at the right apex, anteriorly down to second and posteriorly to fourth space. Fremitus is somewhat increased over this area. Breathing is harsh and respirations slightly prolonged.

Heart. Second aortic accentuated.

The Pulse is regular, rhythmic, of fair volume and high tension. Arterial wall thickened.

Abdomen is rigid; no tenderness, masses, nor free fluid.

Temperature Sense normal, as are the sensations of touch and pain.

Neither the liver, spleen, nor kidneys are palpable.

The Knee-jerks are exaggerated. All reflexes exaggerated. No Babinski nor ankle-clonus.

Stomach Contents. Ewald meal, removed in one hour, 30 cc., thick-yellow fluid with particles of bread. Combined acid 10.

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No free acid; benzidine reaction slowly positive. Microscopic examination shows food particles, starch, many organisms, and yeast. The following day the stomach contents showed a thick yellow fluid with food particles and some mucus. Faintly acid, no free hydrochloric; total acid 20. Benzidine reaction positive. Lactic acid present. Microscopic examination revealed a few bacteria, oil globules, meat shreds, and yeast.

Spinal Fluid. There were 3.5 cc. removed without pressure; clear, no cells.

Blood Examination. Hæmoglobin 80 per cent. (Tallquist.) White blood cells, 6,600; red blood cells, 3,900,000.

(Feb. 6, 1909). Differential Blood Count:

Polymorphonuclears, 80%;

Large mononuclears, 5%;

Small monnonuclears, 9%;

Eosinophiles, 1%.

Red cells stain evenly but are rather pale. Central pale area somewhat exaggerated. Blood platelets decreasd. No polychromatophilia, no poikilocytosis, no nucleated reds, no parasites.

(Feb. 18, 1909). Differential Blood Counts

Polymorpronuclears, 75.3%;

Large mononuclears, 8.3%;

Small mononuclears, 12.6%.

Eosinophiles, 3.3%;

Mast cells, .3%.

Red cells stain evenly but very pale. Central pale area exaggerated. Blood platelets decreased, no polychromatophilia, no poikilocytosis, no nucleated reds, no parasites.

When seen by the present writers, November 12, 1909, the patient was comatose and seemed in a very low condition; she had difficulty in retaining food and was greatly emaciated. The breath was offensive; stamatitis was marked with slight fissures at the angles of the mouth; the tongue was red and glossy with deep transverse fissures. On the backs of the hands and extensor aspects of the wrists the skin presented a dark, slightly corrugated appearance, which was dry and slightly scaly (Figs. 3 and 4). No irritation was complained of nor was there any evidence of scratching. The skin had the appearance of having been repeatedly and for a long time inflamed, with a marked deposition of pigment. Changes in the skin, although to a less extent, were also noted on the elbows and neck. On the latter as well as on the face, the skin bore evidences of

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certain changes which looked as if it had been repeatedly subjected to a mild form of inflammation. This observation was confirmed by members of the family, who said on questioning that the patient had often had a breaking out on the face and neck, although less severe than on the backs of the hands. Being questioned as to the use of Indian corn, they said she was fond of it and had partaken of it freely, but denied that it had ever formed the main constituent of her dietary. The diagnosis of pellagra was made:

First, because the skin lesions looked like those of pellagra.

Second, because the stomatitis had the appearance, especially the deep fissures and glossy plaques on the tongue, of having existed for a long time.

Third, the gastrointestinal disturbances had been complained of for at least five years.

Fourth, the patient's mental state had been, so far as we were able to ascertain, markedly impaired.

The patient gradually failed and died on the 19th of November one week after the case first came under observation.

## Pathological Examination.

For the notes of the gross pathological findings, as well as for material and sections, we are indebted to Dr. W. D. Bretz, of the City Hospital Resident Staff, who performed the autopsy. Microscopic examination has shown the more obvious alterations in the skin to be such as one would expect to find after a persistent erythema. In addition, careful study has brought to light certain changes in the nerves which are worthy of mention, since they give a clue to the production of the more evident lesions of the skin. If examination of other, particularly earlier, cases shall establish the constant occurrence of the nerve lesions noted, a slightly deeper insight into the pathogenesis of certain of the alterations which occur in pellagra will have been gained.

## Gross Autopsy Findings.

External Examination. The length of the body is 124 centimetres, the weight approximately 90 pounds. There is present a marked degree of emaciation, with disappearance of the subcutaneous fat. The skin of the entire body is dry and tightly stretched. All the muscles are considerably atrophied. The dorsum of each hand shows a dry, pigmented skin lesion, extending 2 centimetres above the wrist joint, the upper border being sharply defined at its junction

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with the neighboring more normal skin. The lesion of the right upper extremity is mostly confined to the dorsum of the hand and the lower part of the extensor surface, but the left shows in addition a slight area on the radial side of the flexor surface. The skin is very dry, rough, and fissured, and has a dirty brownish color. Both lesions are symmetrical (Fig. 4).

Lungs. The upper lobes are crepitant, the lower portions of the lungs being considerably firmer. Upon section the upper lobes are œdematous; the lower lobes are consolidated, congested, and œdematous.

The Heart shows little except pallor of the muscle. The right side is dilated. The root of the aorta contains numerous sclerotic plaques.

The Spleen weighs 205 grams and measures 11.00 by 7.5 my 4.0 centimetres. It is slightly adherent to the stomach. The capsule is thickened by an old perisplenitis. The splenic tissue is soft and pale and tears easily. The Malpighian bodies are not visible.

The Liver, which weighs 1,242 grams, measures 18.0 by 19.0 by 7.0 centimeters. The cut surface shows some congestion and a few punctuate areas of hæmorrhage.

The Kidneys show nothing except pallor of the cortex.

The Gastric Mucosa shows numerous small, pea-sized, elevated areas, some of which are hæmorrhagic. Between these polyp-like elevations the mucosa is pale, thin, and glistening. The pylorus is much thickened; its orifice small. The intestines are apparently normal. The mesenteric lymph glands are slightly enlarged, pale and firm.

The Uterus and tubes are normal; the ovaries atrophied.

The Brain, whose weight is 1,240 grams, shows no macroscopic changes.

## MICROSCOPIC EXAMINATION.

Lung. There is a moderate degree of emphysema and most of the alveoli contain serum. Many contain a cellular exudate composed largely of polymorphonuclear leucocytes. A few lymphocytes are present, as well as desquamated, swollen alveolar epithelia in fair numbers. Some of the epithelial cells contain coarsely granular brown pigment. The cellular exudate is most marked in those alveoli immediately about bronchi. The latter contain sero-purulent exudate. The pleura is normal.

The Heart Muscle is markedly fragmented. Many of the muscle nuclei are excessively large. Pigment is prominent.

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AORTA. There is some diffuse sclerosis, together with nodule formation and beginning atheromatosis. In the media there is slight lymphoid infiltration about the vasa vasorum.

SPLEEN. The Malpighian bodies are small and sharply outlined. The pulp is dense, due to proliferation of the stroma rather than of the endothelium. Many of the vessels and trabeculæ are hyalin in appearance.

THE LIVER shows moderate central congestion. The connective tissue is normal and there is no fat. Many of the liver cell nuclei are unusually large and poor in chromatin, but not vacuolated.

PANCREAS. There is considerable congestion. The connective tissue is normal in amount. The cells of the acini are deeply stained. The islands of Langerhans are normal.

THE KIDNEY shows considerable cloudy swelling of the tubular epithelium, and some congestion.

THE SUPRARENALS are normal except for slight congestion. There is no increase in pigment.

THE ESOPHAGUS shows well-marked chronic inflammation of the submucosa, characterized by the presence of many lymphocytes, a few polymorphonuclear leucocytes, eosiniphiles, and fibroblasts.

STOMACH. The mucosa, between the nodular areas noted at autopsy, is very thin and poor in glands. Some of the glands are dilated. The submucosa is thick and dense and contains a few scattered areas composed of closely packed lymphoctyes. About the larger arteries of the submucosa and between the muscle bundles of the outer coats of the stomach there are foci of lymphoid infiltration. The walls of some of the larger arteries of the submucosa are markedly thickened. The nerves of the submucosa are composed almost entirely of elongated, spindle connective tissue cells; none of the essential elements are to detected by the ordinary stains. In the lymph spaces of the outer layers of the gastric wall the endothelial cells are very large, cuboidal, completely filling the lumina of the spaces; the cytoplasm has a bluish tinge. In the pyloric region the submucosa is very thick and shows numerous lymphoid areas like those of the stomach wall. The submucosa is rich in small vessels which show marked endothelial proliferation. The vessel walls are markedly thickened, and about the larger vessels there is lymphoid infiltration, which is eccentric and nodular in some places.

Sections from the small intestine show some congestion of the mucosa and submucosa, slight desquamation of the epithelium and considerable hyperplasia of the endothelium of the small vessels of the submucosa.

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In the mesenteric lymph glands the follicles are very small, but quite prominent because of the depth of stain due to the almost complete absence of germinal centres. Between the follicles the stroma is dense and prominent and there is considerable endothelial proliferation.

Central Nervous System. In the cord and brain many of the ganglion cells are extremely poor in both extra- and intra-nuclear chromatin; they appear exhausted. In the sensory roots of the cord, particularly in the cervical and upper thoracic regions, a fair proportion of the ganglion cells are narrow and decreased in size. In such cells the protoplasm is unusually dense, deeply stained with eosin and contains no Nissl substance. The nuclei are indistinct because of the practically complete absence of chromatin; they are decreased in size and irregular in outline; even the karyosomes may be free of chromatin. The change present in the ganglion cells is quite advance,d and very few stages intermediate between normal sensory ganglion cells and those which show the marked alterations noted are seen. In the brain stem and in the cerebral cortex similar granular, shrunken ganglion cells are seen. Whatever the cause which has produced these alterations, it has very evidently not acted upon the central nervous system uniformly. Ganglion cells immediately adjacent to those most markedly altered may appear quite normal. Furthermore, the sensory cells seem to have been injured to a considerably greater degree than the motor cells. The degree and the exact distribution of the central nervous system involvement can be determined only by an enumeration of the cells from all the various levels of the nervous system, a procedure for which there has not as yet been opportunity.

Skin. Sections from the inner aspect of the radial side of the wrist show, microscopically, a quite appreciable thinning of the epidermis (Fig. 5). Over the summits of many of the popillæ the epidermis averages only six cells in thickness, exclusive of the markedly thickened horny layer. No typical cells of the granulosum type are present. Rather sharply the cells pass over into a superficial layer in which condensation of the cytoplasm has begun and in which the nuclei are very pale (*a*, Fig. 6). This layer passes over into one only a single cell thick in which the protoplasm is very dense, in which definite nuclei cannot be seen and in which the lamella takes a rather deep diffuse nuclear stain (*b*, Fig. 6). Situated upon this is the thickened stratum corneum (*c*, Fig. 6), whose structure varies somewhat in different areas. In places it is made up of numerous dense, completely keratinized lamellæ (*a*, Fig. 5). Elsewhere only the surface portion shows such a very dense structure (*b*, Fig. 5).

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Beneath this is a stratum of varying thickness composed of mesh-like lamellæ separated by spaces (*b*, Fig. 5; *c*, Fig. 6). In these œdematous areas the superficial keratinized zone contains shrunken, irregular nuclear remnants.

The papillæ are much shortened (*a*, Fig. 7), are of varying thickness and in some areas are almost completely atrophied (*d*, Fig. 6). Where papillæ are still present their capillaries are congested and the capillary endothelium is prominent (*a*, Fig. 7). These papillary capillaries can be traced downward to the superficial horizontal vessels of the corium; here, also, congestion and endothelial proliferation are present (*b*, Fig. 7). Where the papillary atrophy is least marked the amount of pigment in the stratum mucosum is moderately increased and in the papillæ chromatophores are present in more than normal numbers.

Beneath the superficial zone of the corium, where the small vessels are prominent because of their endothelial proliferation, the tissue is dense and poor in nuclei. The collagen fibres are thick, many of them almost hyalin in appearance (*e*, Fig. 6). The sweat glands show no change. The elastic tissue, in the deeper regions, is normal. More superficially, many of the fibrils have disappeared, and of those present the majority appear broken and stain very poorly.

In the deeper corium (*c*, Fig. 5) the nerves are very definitely involved. The perineurium may be markedly thickened and rich in narrow, band-like connective tissue nuclei (*a*, Fig. 8). The nerves themselves show rather large numbers of small spindle nuclei, and most of them contain one to three or four deeply pink-stained, round, anyloid bodies (*b*, Fig. 8; *a*, Fig. 9). These are apparently very much swollen and markedly changed nerve fibres. The individual fibres, where they are still to be recognized as such, are increased in size (Fig. 9). With the proper stains only very few axis cylinders can be seen in the cross section of nerves of even considerable size; most of the axis cylinders have entirely disappeared (Fig. 9). Between the nerve and the perineurium is a rather wide space (*c*, Fig. 8).

The pathological changes noted may be summarized as follows:

The gross examinations showed nothing which could be considered very characteristic. The chief points to be recalled are the extreme emaciation, the symmetrical character of the skin lesions, the thickening of the pylorus and the nodular character of the gastric mucosa.

Histologically, also, there is, at first glance, very little that is striking. The skin lesion is atrophic in nature, the gastric mucosa

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shows a chronic atrophic gastritis, the wall of the stomach is the seat of a chronic interstitial inflammatory process and many of the central nervous system ganglion cells appear exhausted.

The epidermis shows rather well-marked atrophy, due to the partial atrophy or almost complete disappearance of papillæ. In addition to the simple thinning of the cellular portion of the epidermis there is marked increase in the thickness of the horny layer, which in places is œdematous and shows nuclear remnants. The normal process of keratinization is disturbed, so that definite granulosum and lucidum layers are not formed. These latter changes are most probably the result of the preexisting congestion.

In the corium there is also well-marked atrophy, with swelling of the collagen fibres and some disappearance of elastic fibrils in the more superficial layers. The disappearance of papillæ is probably the result of the mild chronic vascular inflammation. The most striking alteration is the combined chronic inflammatory and degenerative process in the nerves of the corium. This change is so advanced as to lead to the belief that the nerve alterations are most probably primary, and that the remaining conditions in both corium and epidermis are secondary.

Clinically, pellagra is characterized by symptoms referable to the central nervous system and to the gastro-intestinal tract and by lesions of the exposed skin surfaces. The present case offers a pathological basis for the clinical manifestations, and we believe that the underlying pathological alterations in the central nervous system, skin, and stomach have much in common. The changes in the epidermis and its underlying corium and those in the gastric mucosa and the subjacent submucosa have in common a superficial atrophy and a deeper chronic inflammatory process, the latter most marked about the blood vessels. In both situations the nerves show a combined chronic inflammatory and degenerative process which has led to the disappearance of many axis cylinders.

In view of the fact that pellagra is considered by many to be a toxic trophoneurosis, the nerve cell and nerve fibre changes in this case are of some importance. In our case there is, however, actual structural alteration, so that the term "trophoneurosis" is not exactly applicable. And whether the alterations noted are "toxic" or not cannot be determined. They are non-specific in nature and there is nothing in the local lesions to indicate the action of an infectious agent. Certainly the primary change, in this case at least, would appear to be an involvement of the nervous system, which has led to a loss of ganglion cells and to a disappearance of axis cylinders in the peripheral nerves supplying the skin lesions and

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in those of the gastric submucosa. It seems to us proper to suppose that in this case something—whether an infectious agent or a poison not derived from a living organism we leave beside the question—has attacked primarily the nerve cells, and that the nervous system changes noted are sufficient to account for the group of symptoms which characterized the clinical history; mental impairment, gastro-intestinal involvement and symmetrical skin lesions.

This case is thought to be one of more than usual interest because we are able to obtain a fairly complete history of the disease over a considerable period of time, and that the true nature of the affection remained undetermined. From the hospital notes and the information we were able to elicit from the family it seems evident that the skin and mucous membrane of the mouth had not received the attention they merited. The former was only casually mentioned on the last admission, and in both, their importance in diagnosis seems not to have been duly considered. Such cases are thought to be uncommon in Ohio, nor is it believed that unrecognized pellagra exists to any considerable extent. In conclusion, it is further thought that pellagra, while not wholly confined to certain regions of this country, yet its limitation is fairly well defined, and that from the testimony of those who have seen most of the affection here, it is not entirely new.

## DISCUSSION.

Dr. Babcock said he appreciated the honor of discussing the interesting case reported in Drs. Corlett and Schultz' paper. The speaker said he understood, of course, that there was considerable skepticism in regard to the existence of pellagra in this country, and it was only those who had served in public institptions, particularly in the southern States, and who had been face to face with this condition for years, who could comprehend the importance of having more light shed upon this mysterious malady. A certain amount of the skepticism that had hitherto existed as to the actual presence of the disease in this country he thought had been removed. They had had cases in South Carolina in which the diagnosis had been doubted by the local physicians. Those cases had been thoroughly investigated by men like Dr. James Nevins Hyde of Chicago and Dr. Howard Fox of New York, and now there was no longer any doubt about the presence of pellagra in South Carolina and other States.

A year ago, Dr. Babcock said, a conservative estimate of the number of pellagra cases in the United States placed the number at 1,500. Recently, the figures had been gone over, and it now appeared that the disease had been recognized in twenty-seven or twenty-eight States. While it was most prevalent in Virginia, South Carolina, and the Gulf States, cases of pellagra had been reported in two Illinois hospitals and subsequently in a third, and it had been shown beyond the shadow of a doubt that the disease existed in some of the western States, including California, so that we had now come to the conclusion that it had a very widespread distribution.

Dr. Babcock said that from personal investigation and inquiry he was satisfied that pellagra had existed in South Carolina for nineteen years, at least, while

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a physician with whom he was associated believed it had existed there for thirty years, and there were traditions of cases that went back as far as 1870.

Regarding the mooted question as to the causation of pellagra, the speaker said he did not think it necessary to discuss. Not only were the Italian authorities pushing their investigation along that line, but also the authorities of the United States Government, through Dr. Siler, of the Army, and Dr. C. H. Lavinder, of the Department of Public Health and Marine-Hospital Service, while an English Commission was working along similar lines through Dr. Sambon. This work was largely being done in Italy, while in this country, a few months ago, Dr. John D. Long, of the United States Public Health and Marine-Hospital Service, was sent South and made some investigations of the cases there. He was particularly interested in the microscopic findings in the stools of pellagrins, which revealed the presence of certain intestinal parasites, as amœbæ, etc. In one case that came to autopsy Dr. Long also found some deposits in the foramina of exit of the spinal nerves which he thought might have some bearing on the symptoms in these cases.

Dr. Hyde said that Dr. Sherwell was properly credited with having made the first contribution on this subject to this Association. Dr. Hyde said that in his own paper on the subject, "Pellagra and Some of Its Problems," which was published in the *American Journal of Medical Sciences* for January, 1910, he had made the statement that "it was certain that those who had never consumed corn had had pellagra." Since then he had been in correspondence with Dr. S. M. Sandwith, who had called his attention to the fact that "durra," the original word for millet, is now also often used for maize. The natives did not confuse the two cereals but were usually too lazy to call maize, "durra shammy" (Syrian durra). The speaker added that the statement made above was based largely upon his belief that the natives who ate durra and suffered from pellagra had not been consuming corn.

As bearing upon this subject from a historical standpoint, Dr. Hyde showed an original copy of a volume entitled "Historia Natural y Medica," by Dr. Caspar Casal, which was published in Madrid in 1762, and which, so far as was known, was the first contribution to the subject of pellagra. This book was so rare that a copy of it was not to be found in the Congressional Library or in the Library of the Surgeon General's office.

Dr. Howard Fox expressed his disappointment that he was unable to read a paper, as he had hoped, upon experimental serum therapy in pellagra. At the first Conference on Pellagra held in Columbia two years ago, Dr. M. Ray Powers presented a paper on epizoötic cerebro-spinal meningitis in horses, in which he attributed the cause of the disease to the eating of damaged or mouldy corn. A number of veterinarians who had written on the subject and others with whom Dr. Fox had conversed held a similar opinion. As pellagra was supposed by most authorities to be due to eating mouldy corn, it seemed possible that the serum of an animal recently cured of the above-mentioned disease might be of curative value in treating human beings suffering from pellagra. Dr. Fox had found a mule recently cured from a severe attack of epizoötic cerebro-spinal meningitis or "blind staggers." The animal had kindly been sent by Mr. J. Swinton Whaley to New York, where it had been bled. Dr. Fox had intended to try the serum in a case of pellagra in the service of his father, Dr. George Henry Fox, at the New York Skin and Cancer Hospital. Dr. Babcock had promised to use the serum upon his cases at Columbia, although up to the present the new cases were slow in making their appearance, whereas the old ones had

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either gotten well or had died. As the treatment of pellagra in many cases was hopeless it seemed proper to attempt any method of treatment that was at all rational.

Dr. Babcock, in reply to a question as to the mortality of pellagra, said that in one insane asylum for white people in the South, they had observed the disease, since 1896, in six men and twenty-one women—a total of twenty-seven cases, with eighteen deaths. At the Mt. Vernon Hospital, for the negro insane, they had had sixty-six cases in males and 144 in females, a total of 210 cases, with 121 deaths. The mortality, according to different observers in the South, varied anywhere from 40 to 70 per cent.

As to treatment, Dr. Babcock said that most of the remedies that had been recommended by various authorities had been tried. Extensive experiments were carried on with atoxyl, and some of the earlier cases were apparently benefited thereby. In the case of an old woman who was given very large doses of atoxyl, as recommended by one of the English authorities, atrophy of both optic nerves occurred, possibly as a result of the treatment. Much was to be done, the speaker thought, in the way of diet. Dr. Long was investigating this aspect of the subject; he had found various parasites in the stools of these patients, to the presence of which he was inclined to attribute more or less ætiological significance. Personally, Dr. Babcock said, he believed that these intestinal parasites were of accidental occurrence, and bore no causative relation to the disease, but at the same time, this irritative factor should certainly be eliminated in the treatment of these patients, and the stools should be investigated before any line of treatment was begun. Quinine injections and irrigations had been given by Dr. Long for the removal of the amœbæ. The disease was an exhaustive one, and the treatment should be directed along those lines. In the public institutions, they were learning to treat the disease very much as they did neurasthenia.

Dr. Sherwell said the case referred to by Dr. Hyde was published in *The Journal* for February, 1883. He himself thought the history then given was a typical one of a typical case in the person of an Italian sailor, a Genoese, living as is customary when not at sea, in a hamlet near that city. The symptoms, both subjective and objective, presented a classical picture which he thought was well given in the text, and would enable another to make an almost certain diagnosis in cases of the sort. Two years later a similar case presented itself at his clinic, almost or quite identical, in a sailor also, having the same lethal termination. His opinion expressed then as to ætiology, he did not think he had any reason to change, as he believed it due to fungus intoxication.

It might be particularly noted that these men, as is common with the Italian mariners, had one common mess, but cooked their own polenta, etc., from the grains which they brought from their country homes, so that in reality they were on the same diet as in their native villages. Dr. Sherwell thought that the fungus or parasite to which pellagra had been attributed might occur in all cereals analogous to corn, such as rye, etc.

Dr. Stelwagon stated that apropos of what Dr. Hyde said, several European observers, who had studied this disease, had also made the observation that pellagra had occurred in persons who had never eaten corn. Among this number was Kaposi, and, he believed, Besnier also.

Dr. Hartzell briefly alluded to a case which he hoped to report more in detail later. In Philadelphia he recently had under his observation a girl of nine years, presenting typical symptoms of pellagra, who had never been outside the State of Pennsylvania. Her illness began about a year ago with marked hebe-

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tude; she would remain a long time in one position, and it was almost impossible to direct her attention to anything. Subsequent to this she developed marked gastro-intestinal symptoms, particularly an uncontrollable diarrhœa. Three months ago she developed a marked, brownish-red eruption on the face and on the backs of the hands which ended abruptly at the sleeve, and which was followed by abundant desquamation. The skin generally was slightly pigmented and rough.

Apparently, then, we had a typical case of pellagra occurring in a subject who had never been outside of the State of Pennsylvania, and who, so far as could be ascertained, had never eaten Indian corn, her aunt being quite positive about this.

Dr. Duhring said he had had but little experience with pellagra excepting many years ago in Italy, where he spent some time in Milan and saw many cases. He was impressed at the time with the fact that the erythematous or inflammatory skin manifestations of the disease did not show anything very distinctive. There was considerable infiltration of the skin, but not like that in psoriasis or chronic eczema. In regard to the case referred to by Dr. Hartzell, he had seen that patient on several occasions, and the disease of the skin had impressed him as being distinctly peculiar, and different from that in the cases he had observed elsewhere. There was a symmetrical, low grade inflammation, mingled with distinct brownish pigmentation, and a consequent color which he would describe as an ashy-brownish-coffee-and-milk red. He could not recall having ever seen that color in the European cases, certainly not so pigmented, which was the more noteworthy as the Philadelphia case was a child.

Dr. Duhring said the fact that the eruption occurred so frequently upon the hands and face did not in itself prove to him conclusively that it was due solely or even in great part to the sun's action. He had always been in doubt as to the sun being such a potent factor in this disease. The case Dr. Hartzell reported had not been much if at all exposed to the sun, and the speaker said he would go so far as to say that he believed the sun's influence in this disease had been largely overstated. He believed that the causative factor of pellagra was distinctly internal, and probably of a toxic nature, but he did not care to enter further into the ætiology, as he had nothing new on this subject to contribute.

Dr. Pusey, speaking of the exclusion of corn from the diet, said that when it came to the statement that a patient in this country had never eaten Indian corn, the reliability of such a statement could be seriously questioned. He considered it doubtful that there was any American living at the age of twenty-five who had not eaten Indian corn. The statement was analogous to the contention of Jonathan Hutchinson in regard to the relation between leprosy and eating fish; Hutchinson was always prepared to prove that any one had eaten fish.

Dr. Pusey said that while we had made an important advance in recognizing the presence of pellagra in this country, he was inclined to believe that the diagnosis was now being overworked. Pellagra was not a condition in which we could make as satisfactory a diagnosis as we could in tuberculosis or syphilis. The diagnosis rested on a triad of symptoms—psychic, gastro-intestinal, and cutaneous. It was essentially a picture of autointoxication, such as we met with in gastro-intestinal disturbances, and he believed that many of the cases of so-called pellagra might well be questioned as to the accuracy of the diagnosis. He did not include in this category those well-defined cases which had been

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recognized by experts, but those in which an off-hand diagnosis had been made, based upon the presence of one symptom or another.

With all due respect to many writers on the subject, the speaker said he was inclined to believe that the disease was not of such recent date in this country. Probably many of these cases had been overlooked or unrecognized in the past, especially among immigrants. The speaker recalled a characteristic case recently seen in a Chicago institution, in a patient who had only been in this country six months, and who had certainly had pellagra for a very much longer time.

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PLATE XXIII.—To Illustrate Article by. Dr W. T. Corlett and Dr. O. T. Schultz.

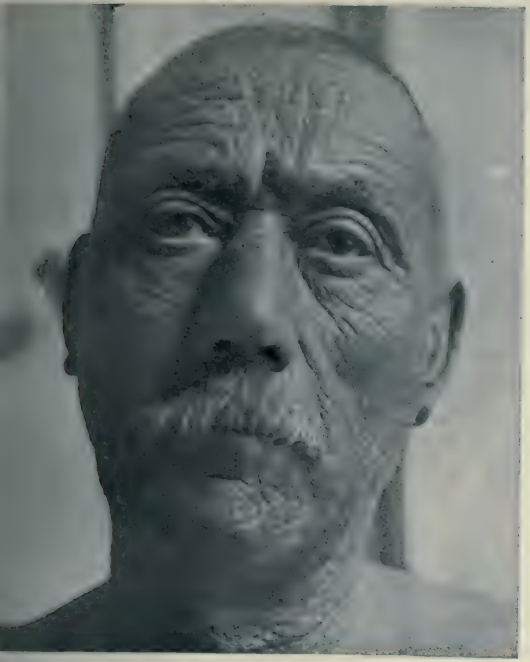

FIG. 1.
Dermatitis simulating pellagra.

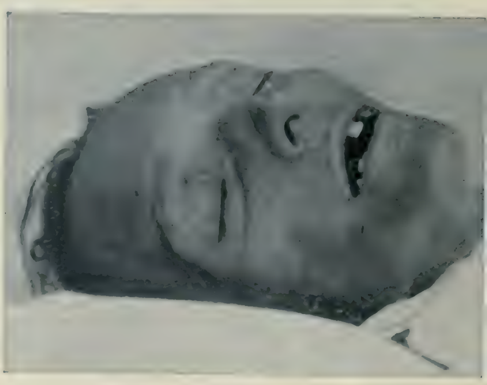

FIG. 3.
Pellagra.
Showing lesions on face, just before death.

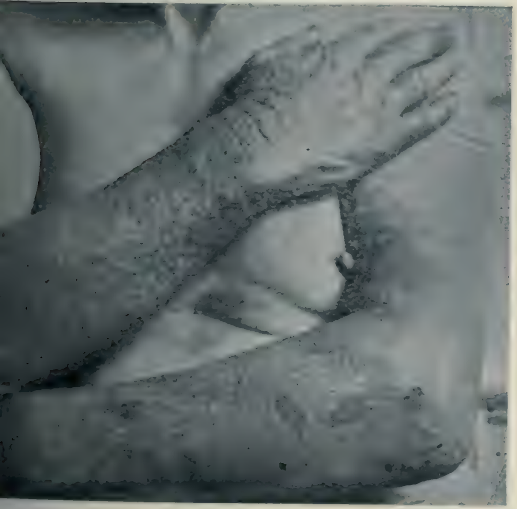

FIG. 2.
Dermatitis simulating pellagra.
ing enlarged papillæ on forearms, quite unlike the
kin of pellagra, which is scaly and pigmented.

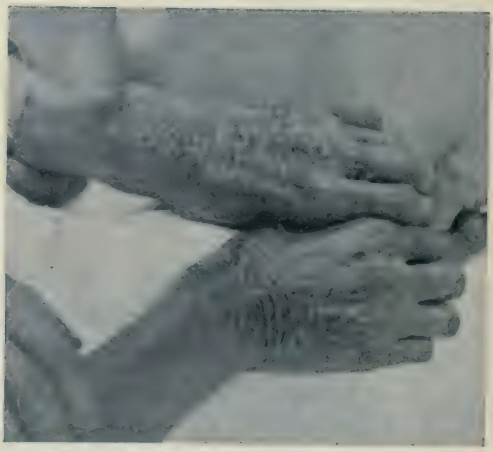

FIG. 4.
Pellagra.
Showing typical lesions on backs
of hands and wrists.

E JOURNAL OF CUTANEOUS DISEASES, April, 1911.

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PLATE XXIV.—To Illustrate Article by Dr. W. T. Corlett and Dr. O. T. Schultz.

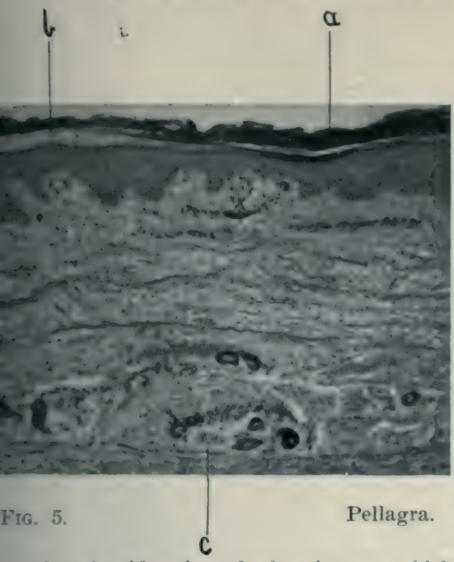

FIG. 5. Pellagra.

trophy of epidermis and of corium. *a*, thick-
d, condensed, hyalin stratum corneum. *b*,
tum corneum, only the superficial layer of
ch is condensed, the deeper portion being
matous. *c*, a nerve.

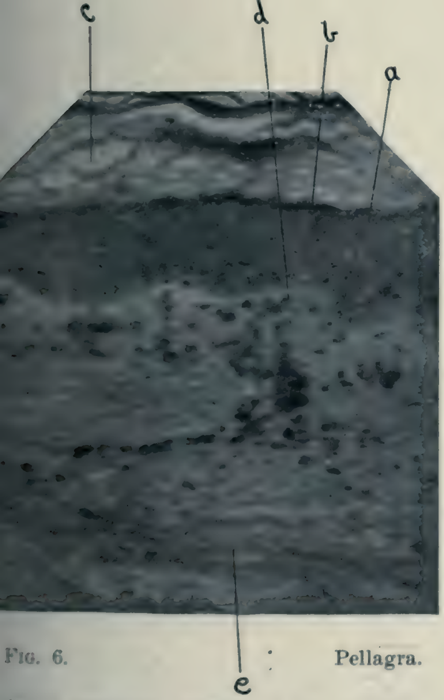

FIG. 6. Pellagra.

lmost complete atrophy of the papillæ. *a*,
nsition zone of stratum spinosum, without the
mation of a stratum granulosum. *b*, a con-
sed lamella rich in diffused chromatin. *c*,
ematous stratum corneum. *e*, hyalin collagen
res.

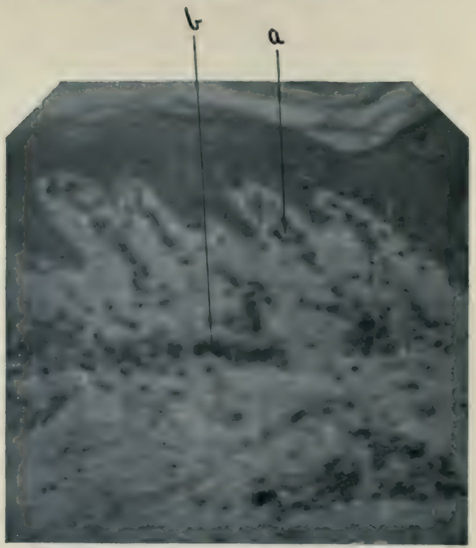

FIG. 7. Pellagra.

An area in which the papillary atrophy is not so marked as in that shown in Fig. 5. *a*, papillary capillary. *b*, superficial vessel of corium. Both vessels show endothelial proliferation.

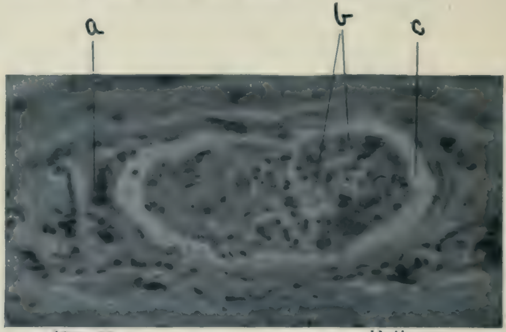

FIG. 8. Pellagra.

Nerve of corium (the same shown at *c* in Fig. 4). *a*, thickened perineurium. *b*, amyloid bodies. *c*, space between nerve and perineurium.

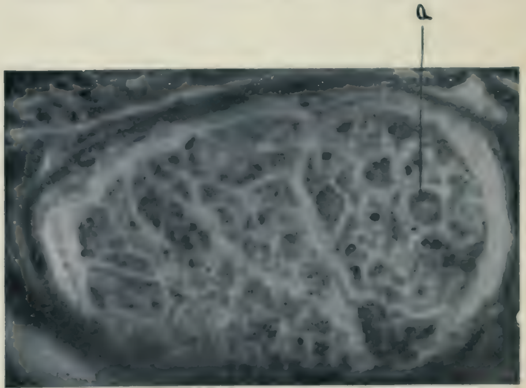

FIG. 9. Pellagra.

The same nerve shown in Fig. 7. Eosin and anilin blue stain for axis cylinders. Most of the axis cylinders have disappeared. *a*, swollen nerve fibre.

No. 7.

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# N MONTHS' EXPERIENCE WITH THE WASSERMAN REACTION AS A CLINICAL SIGN OF SYPHILIS.

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imental Medicine, and the Dispensary of Lake-
de Hospital and Western Reserve University.

[Read before the Ohio State Medical Associa-
n.]

During the last five years the eyes of the medi- l world have been centered on the great problem syphilis, always a deeply interesting disease on ount of its widespread and varying manifesta- ns and up to six years ago, on account of the ystery which shrouded its etiology. In 1905, haudinn[1] announced his discovery of the spiro- etae pallida as the cause of syphilis, and a year ter Wassermann, Neisser and Bruck[2] brought t a serum test for the diagnosis of syphilis. obably nothing since the fundamental discov- ries of Lister and Pasteur has caused such wide- read interest as did these two splendid pieces of rk. Immediately syphilis became one of the est problems in the entire field of internal medi- ne, and the amount of work which has been massed on the subject in the last six years is truly numental. The whole conception of the disease s been changed and we are now able to approach as a definite clinical problem instead of as a antom which must be met on purely empiric rounds.

There is no method of laboratory diagnosis that s received so much attention and criticism and which so many workers have labored as the assermann reaction. The reason for this is ob- us, as syphilis is all encompassing, entering as does into every branch of medicine.

The Wassermann reaction has gone beyond the perimental stage and has become of very definite portance in the careful study of syphilis. So ch has been written on the theory and the thod of performing the reaction and so much ll remains to be said that we shall not enter into discussion of the technical points of this very mplex biological phenomenon. It will only be necessary to refer to the fact that the reaction is sed on the complement-fixation principle of Bor- t and Gengou[3], and that the antigen is an extract liver taken from a human syphilitic fœtus. The st depends on the deviation of the complement in e presence of the antigen and of a positive syph- itic serum. A fact of much interest is that this tigen need not be specific, as in many cases extracts of normal non-syphilitic organs act quite as well as the syphilitic ones. This has caused much criticism of the reaction. Numerous critics claim that if the reaction is not specific it is worthless. In answer to this it must be freely admitted that the reaction is not specific in the sense that Bordet and Gengou used the term; that it depends on the biological phenomena not yet clearly understood. However, the point of issue is, can we depend upon this test for clinical assistance? It is this phase of the question that we have tried to answer.

All observers have found that the reaction occurs in a very large percentage of persons who have or have had syphilis, and that a positive reaction in non-syphilitic states and in normal individuals is extremely uncommon. Certain conditions as leprosy, framboesia, and occasionally scarlet fever, not infrequently give a positive reaction. In the large majority of cases this fact has not affected the clinical value of the test because these conditions are either rare in most parts of the world or are so easily differentiated from syphilis as not to come into consideration in its differential diagnosis. According then to the reports of careful workers in temperate climates the complement fixation reaction occurs in a high percentage of syphilitics and in practically no other condition.

Ten months ago we started to perform Wassermann reactions with the idea of investigating its utility from the standpoint of the clinician. It has been our aim to preserve as far as possible a critical and unprejudiced attitude, and to reach a fair conclusion as to the reliability of this reaction. In this time we have done 1100 reactions on over 900 cases. We have used the original Wassermann technic, dividing the amounts of the various reagents in half as recommended by Swift, and using an alcoholic extract of syphilitic liver instead of the watery extract as first recommended by Wassermann. It is well to remember that the test must be performed by human beings, and that there is a certain small percentage to be allowed for error depending upon human effort. Infallibility cannot be expected. Simply on this ground alone the practice of Kaplan[4] in examining each specimen twice is to be recommended. We feel that a repetition is desirable simply to rule out the error that might occur, for example, once in 500 cases.

We wish to thank Dr. John MacLachlan, Dr. W. T. Corlett, and Dr. John Phillips and the other chiefs-of-clinic of the Lakeside Hospital Dispensary for the large amount of material which they have put at our disposal. Our gratitude is also due to Dr. C. W. Wille of the U. S. Marine Hos-

pital Service, to Drs. E. P. Carter and Chas. W. Stone of the Cleveland City Hospital for the numerous interesting cases from their respective clinics and especially to Dr. G. N. Stewart of the H. K. Cushing Laboratory of Experimental Medicine for valuable aid and suggestions in carrying out our work.

The inquiry in such a series of cases as ours must be: First, what is the frequency of occurrence of the reaction in active and latent syphilis, and does its treatment affect the test or not? Is the reaction expected to occur in cases which are definitely non-syphilitic? Before answering these questions a review of our results in the different classes of cases will be necessary.

### THE REACTION IN NON-SYPHLIITICS.

We have examined 25 individuals who were in perfect health and in whom syphilis could be ruled out. These cases all showed a negative reaction. Further, we have examined 223 cases with numerous other acute and chronic conditions in whom syphilis past or present seemed highly improbable. All these 223 cases reacted negatively except one of scarlet-fever which showed a positive reaction during the first week of the disease. In this case the reaction became negative several weeks later.

In studying the syphilitic cases in our series we have divided the cases according to the stage of the disease. The diagnosis has been made in all cases by highly competent clinical observers, and it has been interesting to us to see how well our results have checked with the clinical findings in most cases.

### PRIMARY SYPHILIS.

The primary stage affords rather variable results. When there was an opportunity to follow the cases by repeating the reaction we have usually found that a positive reaction appeared before the secondary manifestations. The assistance that this gives is obvious. It is unnecessary to allow the patient to become saturated with the specific virus before starting mercury, or on the other hand to place him on what may be an uncalled-for course of mercury simply "to make assurance doubly sure."

E. Lesser[5] reports a case where the blood was examined eight days after exposure and found to be positive. The appearance of an initial lesion and a roseola confirmed the diagnosis. Our earliest reaction occurred on the third day after the appearance of the sore. Unfortunately we have had no opportunity to follow the case.

Ordinarily the spirochæta may be found before the Wassermann reaction appears. Swift, however, calls attention to the fact that if the lesion b in the mouth, the non-pathogenic mouth spir chætes will render the diagnosis uncertain a further that a lesion which has healed before t appearance of the secondaries will make a sear for the spirochætes impossible. Further it is w to remember that one or two applications of cal mel dusting powder to a primary sore frequent will entirely vitiate the results of a spirochæ hunt.

We have examined 28 cases of primary syphili Of these, 23 (82.1%) were positive. It was pos ble in these 23 cases to begin treatment witho waiting for the appearance of the secondary sig The element of time gained is obviously of the u most importance, and if we can advance the da of instituting treatment in upward of 80% of cases of primary syphilis by the use of the Wa sermann reaction we are doing something qui definite.

Among our own cases of primary lues the mo interesting was a man of middle age with an ind lent sore of five weeks' duration on the lower li starting at the junction of mucous membrane a the skin. He had been cut here by a barber. T diagnosis lay between syphilis and epitheliom The reaction was strongly positive. The secon aries might have been masked to appear as me cury had been administered already.

### SECONDARY SYPHILIS.

In the secondary stage the results are mu more striking. Most observers have found b tween 95 and 100% of positive reactions in t stage of the disease. We have examined 91 cas of secondary syphilis, 90 (98.8%) of which gave positive reaction. That considerable clinical a sistance is obtained is evident when one reme bers the number and variety of skin lesions wh may simulate syphilis and the number of atypi secondary manifestations which resemble oth dermatological conditions. This is especially t of women, in whom the initial lesion is oft impossible to find. We recall from our o series a woman with a highly suspicious ra whose physician was unable to find a prima lesion after the most careful search. The rea tion was positive. This finding was checked her husband developing a primary sore later.

### TERTIARY SYPHILIS.

In tertiary syphilis the number of positive rea tions is very nearly as high as in the seconda stage. Of 123 such cases we have found 1 (91.8%) positive. In this period the aid to dia nosis is much greater than in the secondary sta for tertiary signs are notably baffling and a differentiated with much greater difficulty than the secondary signs. In this class of cases we have many with which the internist is confronted, gummata of the viscera, syphilitic disease of the cardio-vascular system, etc., as well as those which face the surgeon, including obscure abdominal conditions and lesions of the bones and joints. We desire to refer to a patient on the medical wards of the Lakeside Hospital with a swelling of the ankle. It was presumably a gumma, but no history could be obtained. The reaction was positive.

### LATENT SYPHILIS.

Latent syphilis is a question of ever-increasing importance. We have classed under this heading those cases in which there were no signs of active disease but which either gave a positive history or showed unmistakable evidences of previous infection, but in whom there were no signs of active disease. We have examined 145 cases of latent syphilis and have found a positive reaction in 91, or 62.8%. The number of positive reactions is of great significance when we stop to think that these patients would be pronounced free from disease on clinical grounds alone, were there no recourse to a serum test. In other words approximately 50% of the cases of syphilis considered cured are in reality carrying infection which is in temporary abeyance, and may become active at any time.

To show that this conclusion is not based upon purely theoretical premises without any pathological confirmation, we may cite Lesser's[5] figures. In over four years' experience in the autopsy room in Berlin, he found tangible evidence of visceral syphilis in 49% of subjects examined, who had given a definite history of lues. This points to the conclusion that in latent syphilis a positive reaction means the persistence of an active focus somewhere in the body. The careful study of such cases by means of the Wassermann reaction is sure to lead to a much fuller understanding of this stage of lues in years to come.

### CONGENITAL SYPHILIS.

Hereditary syphilis is a most interesting problem. It has been found that congenitally syphilitic children who show signs of the disease give a very high percentage of positive reactions. We have examined 20 such cases, and found a positive reaction in 16, or in 80%.

Other observers have reported positive reactions in from 86% to 100% of the cases examined. The reaction has also shown that Colle's law must be revised, or interpreted in a new way. Examination of the mothers of congenital syphilitics, women apparently free from infection, has revealed that many of them have latent syphilis. This would seem to be a most important point and is but another instance of the aid which the reaction has rendered in the detailed story of this most wonderful disease.

Some of our most interesting cases have been those of congenital syphilis. One was that of a child, who was brought to the children's clinic at the Lakeside Hospital. She had a chronic laryngitis and a nasal discharge, and while not healthy in appearance, showed no stigmata of syphilis. On being cross-examined, the mother admitted an infection previous to her marriage, and both mother and child showed positive reactions. The nasal discharge and the laryngitis cleared up under a course of mercury.

Another was that of a young woman referred by Dr. John Lenker. She was 28 years old and of Jewish parentage. The family history was absolutely negative, except that the parents had been married five years before the first pregnancy. There had been no miscarriages. The patient was the oldest child. She had an old interstitial keratitis, marked destruction of the bones of the nose, and necrosis of the long bones. The reaction was strongly positive, and the patient is improving under mercurial injections. The interest lies in the fact that the reaction checked the clinical findings in spite of the history.

### SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.

The syphilitic affections of the central nervous system have been studied very thoroughly. Pearce[6] has collected 630 cases of general paralysis from the literature, of which 81% reacted positively. In the eight cases of paresis studied by us seven (87.7%) were positive. We have studied 28 cases of tabes dorsalis and found that 20 (71.4%) gave positive reactions. This is somewhat higher than the results of the 721 cases collected by Pearce from the literature. In this series 65% reacted positively. Of the 47 cases of cerebro-spinal syphilis examined, 36, or 76.6%, have shown a positive reaction.

It is the opinion of Kaplan,[4] who has done an immense amount of work on neurological material, that the reaction is of much assistance in directing the treatment of tabes dorsalis. He claims that a negative result is a contraindication to urgent treatment, while a positive result may be taken as a symptom of active disease and an indication for pushing treatment. On the other hand a negative reaction in a clinically definite cases of cerebro-spinal lues, especially where the cell-count in the spinal fluid is increased, should not be accepted as an indication for withholding active treatment in this type of case.

It is at once apparent that the number of positive reactions in tabes or cerebro-spinal lues is not as high with this type of the disease as with those we have just discussed. However, positive findings lend considerable aid by confirming clinical findings which alone may be merely suggestive. Such a case came to the notice of one of us in the medical dispensary of Lakeside Hospital. The patient had incontinence of urine in a slight degree. Examination showed eccentric and irregular pupils, reacting little to light but well to accommodation. The knee-jerks were lively; there was no change in sensory perception. There had been a sore on the penis eight years previously, but no secondaries had appeared in the absence of any treatment except cauterization of the initial lesion. A positive Wassermann reaction in both blood and spinal fluid tended to confirm the provisional diagnosis of pre-ataxic tabes or cerebro-spinal syphilis.

The early diagnosis of paresis may be clarified by the Wassermann test, as there is scarcely a condition in which the percentage of positive reactions is so high. This is a most practical point, when one remembers the difficulty encountered in making an early diagnosis of this condition. We recall a case in which the clinical diagnosis of multiple sclerosis had been made, but in which the neurologist's diagnosis of beginning paresis was confirmed to a certain extent by a positive reaction.

It has been interesting to note, that in most cases where the blood serum gave a positive reaction, the spinal fluid was also positive, and vice versa. Occasionally, however, one encounters cases where the blood gives a negative reaction, while the spinal fluid gives a positive result. Though these instances are rare, they are important, and serve to call attention to the desirability of making the serological test with both blood-serum and spinal-fluid when feasible. In illustration of this Osborn[7] has recently reported a case where the only signs were a slight dilation of the left pupil and tremor of tongue. The Wassermann reaction performed by us upon the blood was negative, while that upon the spinal-fluid was positive. The spinal-fluid also showed an increase in the lymphocyte content. Of course cases of this type are important ones to detect.

### CASES WITH QUESTIONABLE HISTORY.

Thus far we have analyzed from our own cases those which are definitely syphilitic and those definitely non-syphilitic. The cases in which on one hand syphilis could not be fairly excluded, or on the other hand, in which a negative history was given and the physical signs were open to question, have been placed in a separate division. This includes 87 doubtful cases, of which five gave positive reactions. Two were arteriosclerotics in which a history of syphilis could not be secured. One was a patient suffering with a tumor of the stomach; she had had at least one miscarriage, and showed improvement under potassium iodid. Then there was an individual with a history of promiscuous living. He denied that he had had an initial lesion, but had had two attacks of gonorrhea, one lasting for a year. About two years ago he had a reddish eruption over the entire body. The reaction was strongly positive. The probability of an urethral chancre at once suggests itself. There was also a case of gout, with a very vague history.

### CONSTANCY IN RESULTS.

We feel that it is desirable to recount the following instances. Early in our work, we examined a specimen from a man with a dubious history of infection. We considered this result as faintly positive, for while there was a marked hemolysis, a certain proportion of undissolved cells remained. Two subsequent tests were quite negative. This was simply a mistake in reading the first end-result, and was to be attributed to inexperience. We might quote a similar experience in examining a case for Dr. W. T. Corlett. In our entire series of 1100 reactions, we have only one other case in which a positive result was obtained at one time and a negative later, with no change in treatment in the interval. The latter result we attribute to the fact that different antigens were used for the two examinations, for it is well known that antigens vary slightly in delicacy, a point mentioned by Swift. To this same fact may be attributed the discrepancy which is seen occasionally between the results of different laboratories.

### EFFECT OF TREATMENT UPON THE REACTION.

A question of vital interest is the behavior of the reaction under treatment. Of course, it is much too early for anyone to draw final deductions from the facts at hand. Indeed, positive rules cannot be formulated until years have elapsed and there has been ample opportunity to observe, for at least two generations, the offspring of luetic parents who, to all appearance, had been cured.

We have, however, learned a great deal about treatment. Mercury is the only drug which has a marked, constant, and dependable effect upon the reaction. Potassium iodid influences it very little.

From the standpoint of converting a positive reaction to a negative, mercury is much more efficient when given by inunction or injection than by mouth. We have examined a patient who had had mercury by mouth for as long as nine years and who still gave a positive reaction. It has been no at all unusual in our experience to encounter patients who had taken by mouth either the bichloride or the protoiodide of mercury almost constantly for three, four and five years, and who still gave a positive reaction. Furthermore these patients were in many instances extremely intelligent men who understood their own situation thoroughly and were making every effort to cooperate in their own treatment. The mercury was often taken to a point of salivation.

Salvarsan may change a positive reaction to a negative, but our own experience (which coincides with that of other workers) is that eventually the reaction again becomes positive and remains so until further treatment is instituted.

We had the privilege of following for Dr. W. T. Corlett thirteen cases which had been treated with salvarsan. Three of these were examined before the administration of the drug and not again for an interval of two or three weeks. The reaction was still positive. A fourth case received a intravenous injection in New York. With him the reaction was positive a few days later, also six weeks, and again eight weeks after injection. The remaining eight cases were examined once a week for several weeks and some have been examined since. Five remained positive throughout, the last serological tests being made on the twelfth, the third, the fourth, the fifth, and the sixth weeks respectively after injection. One case with a very weak reaction became negative after a second injection of the drug. With another patient, who showed marked clinical improvement, the reaction became negative on the fifth week, but returned to positive and was still positive on the twelfth week. The last patient was the most interesting of all. His reaction became negative during the first week, but was positive the next week and remained so until the seventh week, when it became negative. He has not been examined since.

During the last two months we have examined eight cases treated with salvarsan by Dr. C. W. Wille, in charge of the United States Marine Hospital in Cleveland. None of these cases show a negative reaction at the present writing. The time of last examination ranged from two to nine weeks after injection. It is but fair to say that almost all the cases cited above are severe, chiefly in the late secondary or tertiary stage. We have examined for Drs. Tarr and Staral one case of primary syphilis of mild form, who developed a Wassermann reaction four weeks after the appearance of his sore, and who had had no secondary manifestations. He received salvarsan, and now ten weeks after injection his Wassermann reaction is negative. It will be interesting to follow this case, to see if perhaps we have one of the salvarsan cures.

On the whole our general impression from these cases has been that salvarsan has little permanent effect upon the reaction in most cases.

A rule for pronouncing patients cured, which seems excellent in the light of present knowledge, is to have the reaction done four to six weeks after the last dose of mercury. If negative, treatment is withheld and the reaction is repeated in one month, again after an interval of three months, and finally at the end of a year.

In summing the present feeling in regard to the reaction as a guide to treatment, we can do no better than to quote Swift[8]:

> "1. As soon as a positive reaction appears in primary syphilis treatment should be instituted. The reaction with the presence of spirochæta pallida, renders a diagnosis positive, and by starting treatment before the appearance of secondary symptoms a dangerous saturation with the virus will frequently be avoided, and the danger of the patient becoming an active distributor of the spirochæta minimized.
>
> "2. In the first three years of the disease treatment can be more rationally controlled, than by merely following the rule of a certain amount of treatment, with periods of rest. By means of frequent observations, in many cases, the disease can be controlled with a small amount of mercury, while others will require constant application to treatment.
>
> "3. In the late latent period a positive reaction is an indication for further treatment, and, as a rule, treatment should be continued until the reaction becomes negative. This rule should, of course, be modified according to the condition of the patient. If he tolerates mercury badly, or presents other contraindications to treatment, the indications for the individual case must be recognized and met. Perhaps some reactions never yield, but it is in such cases that the prognosis is probably bad and such patients that we may expect to go on to tabes or general paralysis. A persistent negative reaction is a good prognostic sign: a returning reaction is a warning that a relapse may be imminent, and is sufficient indication for renewal of treatment."

CASES DEFINITELY SYPHILITIC.

| Stage | Total Number | Number Positive | Percent Positive |
|---|---|---|---|
| Primary | 28 | 23 | 82.1 |
| Secondary | 91 | 90 | 98.8 |
| Tertiary | 123 | 113 | 91.8 |
| Latent | 145 | 91 | 62.8 |
| Cerebro spinal | 47 | 36 | 76.6 |
| Paresis | 8 | 7 | 87.5 |
| Tabes | 28 | 20 | 71.4 |
| Congenital | 20 | 17 | 85.0 |

### CONCLUSIONS.

To sum up, we would conclude from our experience that:

(1) The technique of the Wassermann reaction is extremely difficult. Its performance requires the resources of a well-equipped laboratory. Re-

actions should not be performed singly but a considerable number should be done at the same time in order to provide sufficient controls. The reading of doubtful results is occasionally difficult. Therefore, considerable experience is essential.

(2) In this climate a positive result may be taken as a specific sign of syphilis in at least 99% of cases. In the remaining 1% cases, syphilis usually cannot be excluded completely. In other words, we wish to emphasize the point that a positive reaction is a more definite and a more positive symptom than any previously at hand.

(3) A single negative reaction carries much less weight, and cannot be taken as positive evidence against syphilis. Repeated negative reactions may, however, be construed as negative evidence when weighed with the other clinical findings.

(4) Repetitions of the reactions are desirable for the sake of confirming findings.

(5) The result of the reaction is of very great assistance in the treatment of syphilis, but should be interpreted by one who has had experience with both the clinical and and the serological side of the question.

(6) As is true with all laboratory tests, this reaction cannot take the place of careful clinical observation, but properly interpreted will aid the clinician greatly.

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# ACUTE YELLOW ATROPHY OF THE LIVER IN CHILDREN, WITH REPORT OF A CASE.

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Acute yellow atrophy of the liver is a very rare disease. In fact, Osler[1] states in the third edition of his *Practice of Medicine* that he had never seen a case. Rolleston,[2] in twenty years had seen in the postmortem room or examined the liver of 7 cases. It occurs much less frequently in children than in adults, and for that reason the following case is considered worthy of report.

G. R., a female child, aged five years, was admitted to the children's ward of Lakeside Hospital, November 3, 1909, suffering from intense jaundice associated with stupor. Neither the family nor the personal history threw any light on the case. One week before admission she began to lose her appetite, and vomited several times a day, the last time she vomited being two days before coming to the hospital. During this time the child became more deeply jaundiced, the stools were clay colored, and the urine a deep yellow color. The parents stated that they had not noticed any blood in the vomitus or in the stools. During the last twenty-four hours she had been unconscious.

Physical examination showed a well-developed and quite well-nourished child, tossing about restlessly in bed. The skin and mucous membranes were deeply jaundiced, a small ecchymotic area was noticed in the left lower quadrant of the abdomen, and another on the outer side of the right arm just above the elbow. There were numerous small petechiæ over the lower extremities below the knees. The child was unconscious, but seemed hypersensitive when touched. The pupils were widely dilated and reacted sluggishly to light. The ears, nose, and throat were normal, but the tongue was heavily coated with a yellowish-white fur. Slight general glandular enlargement was noted. The temperature was 96.2° by rectum, the respirations were 30 to the minute, and somewhat shallow and irregular. Examination of the lungs revealed nothing abnormal. The pulse rate was 64; with the exception of some arrhythmia there was nothing of importance in the examination of the heart. The abdomen was somewhat distended, especially in the lower part, this being due to a full bladder. The spleen could be felt. The lower edge of the liver was not palpable; the upper border of hepatic dulness began at the fourth rib in the right mammary line, and at the sixth rib in the axillary line. The tendon reflexes were exaggerated, and there was some spasticity of the legs. The urine was dark yellow in color; specific gravity, 1017; alkaline, contained a faint trace of albumin, and bile was present in large quantity. The microscopic examination of the centrifugalized sediment showed many epithelial and hyaline casts and many leucin crystals. The leukocyte count was 22,400.

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[1] Practice of Medicine, 3d ed.

[2] Diseases of the Liver, Gall-bladder, and Bile-ducts, 1905.

The child vomited shortly after admission to the hospital, the vomitus being mixed with dark clotted blood. The stomach was then washed out and numerous blood clots came away in the washing. The child died two hours later.

AUTOPSY REPORT. *Anatomical Diagnosis.* Acute yellow atrophy of the liver, icterus, petechial hemorrhages (skin, omentum, mesentery, mediastinal tissues, epicardium, pleura, lung, Peyer's patches, mucous membrane of the stomach), cloudy swelling of heart, kidney, pancreas, and adrenals, stenosis of the cystic duct, thyroid hyperplasia.

Autopsy was performed nine hours after death. The body was that of a well-formed female child, 95 cm. in length. Postmortem rigidity was slight. There was marked postmortem staining over the dependent parts, with numerous petechial spots on the extremities below the knees. The skin everywhere was markedly icteric, the conjunctivæ bright yellow, the pupils widely dilated and equal. A dark brownish fluid was exuding from both nostrils; the ears were free from discharge. The superficial fat was moderate in amount and bright yellow in color.

The peritoneum was smooth. The fat everywhere, omental, mesenteric, and in appendices epiploicæ, showed numerous hemorrhages varying in size from a pin head to a dime. The hemorrhagic condition in the mesentery was very striking, and seemed to be equally distributed throughout, being most marked toward the attachment to the gut. The liver was small, pale in color, its lower border lying well above the margin of the ribs. The gall-bladder, ducts, and the appendix appeared normal. There was a small amount of free bile-stained fluid in the peritoneal cavity. There was nothing abnormal about the diaphragm.

Both pleural cavities were free from adhesions, and contained a small amount of bile-stained fluid. Beneath the visceral pleura, numerous small hemorrhagic points were noted; these were also quite numerous in the mediastinal fat and in the fat of the epicardium. The pericardium contained a small amount of bile-stained fluid; there were no adhesions, and no subpericardial hemorrhages. The heart weighed 70 grams. The valves were normal; the endocardium was bile stained, but there were no hemorrhages beneath it.

The right lung weighed 170 grams, crepitant and air containing throughout. The surface was smooth and mottled with small dark red areas. On section throughout the lung substance, varying in size from a pin point to 2 cm. in diameter, were numerous small hemorrhages; the bronchial mucosa was slightly congested. The left lung weighed 160 grams, and showed the same conditions as the right except that the hemorrhagic areas were more numerous. The bronchial lymph glands were not enlarged.

The colon was normal. The ileum showed nothing of note except a hemorrhagic Peyer's patch just above the ileocecal valve. The duodenum showed some congestion just above the papilla of the common bile duct. The bile ducts were normal with the exception of the cystic duct, which was occluded 2 cm. from its origin in the gall-bladder. The walls of the stomach were covered with a large amount of thick mucus, and there were a few small hemorrhages into the mucosa along the greater curvature.

The liver weighed 250 grams, was pale in color, very flabby, and showed some wrinkling of its capsule. It lacked the rigidity of a normal liver, and partially collapsed and bent under its own weight. On section, the lobular markings were indistinct, and showed bright yellow areas 1 to 2 cm. in diameter, mingled with reddish slightly depressed areas. The outlines of the lobules were entirely lost in the red and could only occasionally be discerned in the yellow areas. The gall-bladder contained a small amount of bright yellow mucus, and the walls were slightly congested. The pancreas was normal.

The right kidney weighed 80 grams. The capsule stripped readily, leaving a smooth surface, fetal lobulation was well marked. On section, the cortex was swollen, and showed marked cloudy swelling. The left weighed 75 grams and was similar to the right.

The thymus was normal. The thyroid was slightly enlarged. The trachea and larynx showed no submucous hemorrhages.

The brain weighed 1075 grams. The calvarium showed marked depressions, every convolution of the cerebrum being marked by a corresponding mould in the inner table of the skull. The dura mater showed definite bile staining. The section of the brain showed nothing unusual.

On microscopic examination, the liver showed extensive degeneration. In many sections no trace of liver cells could be seen, nothing being left but the vascular stroma. In other sections traces of liver cells still remained, but the cells were granular, vacuolated, and stained diffusely; an occasional cell could be seen which stained well, these having a granular vacuolated cytoplasm and a small darkly stained nucleus. There was no evidence anywhere of regeneration of liver cells. In the areas where the degeneration of liver tissue was most marked, the capillaries were distended with blood. Hemorrhages were quite numerous. The interlobular bile ducts showed everywhere a marked proliferation; this was most marked in the areas where the destruction of the liver cells was greatest. Here the lobules were completely surrounded by proliferated connective-tissue of Glisson's capsule in which were numerous newly formed bile ducts. These showed a tendency to spread down into the lobules in places, which was evidently an attempt at regeneration. Glisson's capsule showed a slight round-celled infiltration, and was everywhere thickened, in some places considerably so. The gall-bladder was normal; desquamated epithelial cells filled the lumen of the bile ducts. The heart showed nothing but a considerable grade of cloudy swelling. In the lungs a few small areas of focal hemorrhage were seen. There was nothing else abnormal. The thymus was normal. The thyroid showed a moderate grade of hyperplasia. A moderate degree of cloudy swelling was found in the adrenals. The brain was normal.

Cultures taken from the heart blood gave a pure growth of staphylococcus albus. Sections of the liver stained by the Levaditi method failed to show spirochetes.

In 1894 William Hunter was able to find 250 published cases of acute yellow atrophy of the liver. Four years later McPhedran[3] collected 29 additional cases. In 1903 Best,[4] in an exhaustive study, found about 500 cases reported in the literature. Of these, a small proportion occurred early in life. I have been able to find reports of 40 children with this disease; these including my own patient making a total of 41. In 1905 Rolleston was able to collect 22 cases in the first ten years of life.

One of the earliest cases recorded was that of Politzer,[5] who, in 1858, observed this condition in a newborn infant. On the fourth day after birth the child became ill with jaundice and bloody vomit, which became worse on the following day, and was accompanied by high fever and restlessness with a tendency to stupor. Later the left lobe of the liver showed a perceptible diminution in size. On the eighteenth day the child died, death being preceded by convulsions and bleeding from the umbilicus. The urine showed leucin and tyrosin cyrstals. The liver at autopsy was considerably diminished in size, the diminution chiefly affecting the left lobe. The bile passages were patent and the umbilical veins and arteries were normal. The microscopic examination of the liver showed a high degree of destruction of the liver cells. The same author, two years later reported a case in a girl baby four months old, who

[3] Sajous' Annual, 1899, iv, 393.

[4] Thesis, Univ. of Chicago, 1903.

[5] Jahrb. f. Kinderheilkunde, 1860.

became suddenly ill with diarrhea, vomiting, and fever, the symptoms suggesting a gastro-intestinal catarrh. On the seventh day of the illness, icterus appeared, which became very intense. The stools were free from bile pigment. The liver was enlarged and painful on pressure. This increased liver dulness continued until the twelfth day. On the fourteenth day there was evident diminution in the size of the liver, blood was vomited and passed with the stools. Forty-eight hours later the child died from exhaustion, and by this time no liver dulness could be made out below the costal margin. An autopsy showed that the liver was small and flabby, and microscopically there was great destruction of liver cells, the latter containing a great deal of fat.

The following cases have been reported by various authors: Loeschner,[6] boy, aged three years; Mettenheimer,[7] boy, aged four years; Widerhofer,[8] girl, aged one and three-fourths years; Hecker,[9] newborn girl; Senator,[10] girl, aged eight months; Brandenburg,[11] boy, aged eleven weeks; Hilton-Fagge,[12] boy, aged two and one-half years; Steiner,[13] boy, aged ten years; Monti,[14] boy, aged four years; Pleischl and Falwarczny,[15] boy, aged fourteen years; Mann,[16] boy, aged one and one-fourth years; Aufrecht,[17] newborn child, Dinkler,[18] girl, aged twelve years; Brunton and Tunnicliffe,[19] boy; aged three and one-half years; Foltanek,[20] boy, aged twelve years; Goodhart,[21] boy, aged two and one-half years; Bjelin,[22] child, aged thirteen years; Greves,[23] child, aged one and three-fourths years; Babes,[24] boy, aged six years; Lewitsky and Brodowsky,[25] child, aged fifteen years; Lanz,[26] boy, aged four years; Meder,[27] boy, aged fifteen years; Merkel,[28] boy, aged six years; Poddig,[29] boy, aged two and one-half years; Rehn and Perlo,[30] boy, aged two and one-half years; Rinsema,[31] girl, aged five years; Rosenheim,[32] girl, aged ten years; Heukelon,[33] child aged three months; Starck[34], boy, aged two and one-half years; West,[35] boy, aged six years; Schmidt,[36] boy, aged two and one-fourth years; Todt,[37] girl, aged three and one-yalf years; Carpenter,[38] girl, aged twenty-three months; Rogers,[39] boy, aged four years; Parkinson,[40] boy, aged four years; Wentworth,[41] boy, aged five years; Griffith,[42] boy, aged seven years; Drennan,[43] boy, aged eight years. The proportion of boys and girls afflicted is approximately two to one.

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[6] Oesterrichische Zeits. f. Kinderheilkunde, 1856. (Abstract, British and Foreign Medico Chirurg. Review, 1860, vol. xxv.

[7] Memorab. aus der Praxis., 1862, vol. vii.

[8] Jahrb. f. Kinderheilkunde, 1859, Band ii, p. 42.

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[12] Trans. Path. Soc., London, 1869, xx, 212.

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[16] Amer. Jour. Obstet., 1875, viii, 539.

[17] Zentralbl. f. innere Med., 1896, No. 2.

[18] Inaug. Dissert. Halle, 1887.

[19] St. Barthol. Hosp. Rep., 1896, xxxii, 425.

[20] Quoted by Merkel.

[21] Trans. Path. Soc., London, vol. xxxiii, p. 82.

[22] Quoted by Merkel.

[23] Brit. Med. Jour., 1884, i, 766.

[24] Virchow's Archiv, 1894, No. 136.

[25] Quoted by Merkel.

[26] Wien. klin. Woch., 1896.

[27] Ziegler's Beiträge z. Path. Anat., 1895, Band xvii, S. 143.

[28] Münch. med. Woch., January 30, 1904.

[29] Inaug. Dissert. Königsberg, 1892.

[30] Berl. klin. Woch., 1875, S. 644.

[31] Quoted by Merkel.

[32] Zeits. f. klin. Med., 1889 Band xv.

[33] Nederl. Tijdschr. v. Geneesk., 1888.

[34] Jahrb. f. Heilkunde, 1898.

The etiology of acute yellow atrophy of the liver is quite unknown, but it is probably not due to a specific poison, for we find that numerous forms of intoxication, particularly chloroform, phosphorus, syphilis, alcohol, puerperal eclampsia, may lead to a condition closely resembling this disease. I have seen one case of chloroform poisoning in which the symptoms and the course of the disease were indistinguishable from acute yellow atrophy of the liver, and leucin and tyrosin crystals were found in the urine. Inasmuch as there is such a marked resemblance between this disease and phosphorus poisoning, some writers have thought that all cases were due to poisoning with phosphorus, but that is not true, as recent pathological studies have served to differentiate between the two conditions. Wells[44] has summarized the chief differences between phosphorus poisoning and acute yellow atrophy as follows: "Phosphorus produces a general injurious effect upon all the organs of the body, the liver merely showing the most marked anatomical changes, which at first consist of fatty metamorphosis of the liver, due to a migration of the body fat from the fat deposits into the injured cells, subsequently the liver cells disintegrate, the cytoplasm being affected before the nucleus, and the liver may become smaller than normal, although it is usually enlarged because of the fat deposition. Typical acute yellow atrophy is characterized by an early necrosis of a large proportion of the liver cells, the nucleus becoming unstainable while the cytoplasm is still little altered in appearance, and fatty changes play a subordinate role or are absent. As Auschutz says, "The poison seems to strike at the life of the cell, its nucleus, while phosphorus attacks the cytoplasm. Furthermore, the poison of yellow atrophy seems to be very specific, for it attacks the other organs of the body almost not at all, and within the liver it affects only the hepatic cells proper, while the bile duct epithelium and stroma cells are so little injured that they are able to proliferate greatly, this proliferation being a prominent feature."

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[35] Trans. Path. Soc., London, 1880, xxxi, 116.

[36] Inaug. Dissert. Kiel, 1897.

[37] Akute gelbe Leberatrophie im kindlichen Lebensalter, Berlin, 1903, p. 32,

[38] Reports of Soc. for Study of Disease in Children, London, v, 133, 134.

[39] Reports of Soc. for Diseases in Children, 1906, vi, 294.

[40] Report of Soc. for Study of Disease in Children, London, 1906, vi, 229.

[41] Archives of Pediatrics, February, 1906, p. 81.

[42] Archives of Pediatrics, February, 1906, p. 88.

[43] Jour. of Path. and Bact., July. 1911, p. 141.

[44] Chemical Pathology, 1907.

Wells further considers that the atrophy is due to an autolysis of necrotic liver cells by their own enzymes, and that in the most typical cases of acute yellow atrophy we have to do with a poison having a very specific effect on the liver cells, which destroys their synthetic activities without injuring their intracellular proteolytic enzymes, and consequently autolysis occurs. The fact that so many cases are preceded by symptoms of gastro-intestinal disturbance would lead us to suppose that this poison was of intestinal origin. Quincke considered that possibly regurgitation of pancreatic juice up the bile ducts might be responsible for the degenerative condition in the liver, but this is not true, for the bile pressure is greater than that of the pancreatic juice, and the bile ducts and peripheral portions of the lobules are always least affected. Klebs, Eppinger, and others have ascribed a bacterial origin to this disease, basing their conclusions on the finding of bacteria in the bile ducts and liver detritus in fatal cases. The bacteria in these cases were probably secondary invaders. In a case reported by Aufrecht, the disease in a newborn infant was associated with a sclerema neonatorum.

Acute yellow atrophy may occur in chronic drunkards, the condition supervening on existing cirrhosis. It may also occur in secondary syphilis. In a case reported by Merkel, though the child showed no signs of syphilis, the father had a syphilitic spastic paralysis of the lower extremities, and the mother had had repeated abortions. The disease is commonest between the ages of twenty and thirty in adults, females being more often attacked than males, in the proportion of 2 to 1, in contrast to the condition we see in children, where males are more frequently affected.

The majority of cases run their course in two weeks. Occasional cases occur in which the disease is spread over many weeks or months. In general we can divide the symptoms into two stages. The first, which lasts five or six days or sometimes much longer, is characterized by malaise, often muscular pains, nausea, vomiting and occasionally diarrhea, at other times constipation. The jaundice appears during the latter part of this stage. Often the jaundice is the first sign, increasing steadily in its intensity. Cases of acute yellow atrophy have been described in which no jaundice was present.

The second stage is marked by the pronounced grave change in the patient's condition, and especially by the appearance of nervous symptoms, severe headache, intolerance of light, restlessness, delirium, twitching of the muscles, convulsions, coma. In this stage transient paralyses sometimes occur, so that, excluding the jaundice, the clinical manifestations may closely resemble meningitis.

With the onset of the second stage the vomiting becomes more severe and the vomitus often contains blood. The tongue is dry, brown, and tremulous, and the teeth covered with sordes. The pulse is rapid and of low tension. The respirations are often quite irregular. The temperature is often elevated; in other cases it is depressed, rising just before death. Often petechiæ and hemorrhages are found beneath the skin, and blood may be passed in the stools and urine. Epistaxis occasionally occurs. The liver at first may be increased in size, but, as a rule, the liver dulness is much diminished before death, this diminution being partly due to the change in size of the organ and partly to its flabbiness, allowing it to fall away from the abdominal wall, the coils of intestine taking its place. The spleen is sometimes enlarged. The urine contains a great deal of bile and, as a rule, albumin and casts. It is remarkable that glycosuria is not observed. The urea is diminished, but the percentage of nitrogen present as ammonia is increased. Leucin and tyrosin are nearly always present, sometimes one being present in the urine without the other. There is nothing distinctive about the blood. Leukocytosis is nearly always present, and in a few cases colon bacilli have been found by blood cultures. The coagulability of the blood is decreased.

*Morbid Anatomy.* The liver is always greatly diminished in size, often weighing only one-half to one-third of the normal weight. The liver is more or less universally affected, but often the left lobe shows the most marked atrophy, as in the first case reported by Politzer. In the chronic cases where the disease has existed for months the surface of the liver, instead of being smooth, is nodular, due to a compensatory hyperplasia of the liver cells, comparable to the adenomata seen in cirrhosis. The capsule is wrinkled and loose, and small hemorrhages may be seen beneath it. The liver is flabby, so that it bends readily under its own weight. Its surface is greenish yellow in color, with here and there reddish areas. It cuts with resistance. The cut surface is a bright lemon-yellow color, with numerous patches of darker brownish red, the latter predominating in the left lobe, where the greatest atrophy is seen. The yellow areas are soft and slightly swollen, the reddish areas are tough and of a leathery consistency. Histologically the change in the yellow areas are seen to be more recent, the parenchymatous cells showing extensive fatty changes, the fat droplets being within the nucleus, as well as within the cytoplasm. In the red areas, absorption of the fatty material has taken place, and we see mainly a network of capillaries, within the meshes of which are degenerated liver cells and the detritus of broken-down liver cells, masses of chromatin, and blood. When death has been delayed, evidence of regeneration can be seen in the form of patches of newly-formed liver cells, with deeply staining nuclei, some of them exhibiting mitoses. Pseudo-bile capillaries may also be present in considerable number. Crystals of leucin and tyrosin may be seen in fresh sections, and the amount of fat which can be extracted from the liver is about 5 per cent. above the normal. The gall-bladder contains bile mixed with a great deal of mucus, and the bile ducts are normal.

The kidneys and heart show evidences of cloudy swelling, and the spleen is softened and enlarged.

The gastro-intestinal tract usually shows evidences of catarrhal inflammation. There is often some ascites.

Petechial hemorrhages may be found beneath the pleura and pericardium, and in the intestinal mucosa, and sometimes extensive cerebral and meningeal hemorrhages occur.

The diagnosis is usually simple from the intense jaundice, the nervous symptoms, the atrophy of the liver and the finding of leucin and tyrosin crystals in the urine. The latter are sometimes seen in other conditions of the liver, where there are marked degenerative changes. Sometimes these cases are confused with cases of phosphorus poisoning, but a careful history will serve to distinguish the latter. Hilton-Fagge has recorded a case in a boy, aged two and one-half years, where the symptoms were incorrectly thought to be due to belladonna poisoning.

Acute yellow atrophy of the liver is almost uniformly fatal. A few cases of undoubted recovery have been recorded. In 1897 Wickham Legg gave a list of 28 reported cases of recovery.

There is no treatment of much avail. Free purgation, intravenous or subcutaneous transfusion with saline solution, and intestinal antisepsis have been recommended.

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# A Case of Phlebitis Migrans

## A Case of Phlebitis Migrans.

By JOHN PHILLIPS, M. B., Assistant Professor of Medicine, Western Reserve University, Cleveland, Ohio.

The occurrence of extensive recurring phlebitis is very uncommon. In 1905, Briggs collected from the literature four cases and reported three others that came under his personal observation, in which no etiological factor could be determined, and suggested the title of "Idiopathic Recurrent Thrombophlebitis." One of the earliest reports is that of James Paget in 1866, who described certain cases of migrating phlebitis, associated with ordinary gouty inflammation in the foot or joints, and occurring, with little or no evident provocation, in persons of marked gouty constitution or with gouty inheritance. His description is so accurate that I give it in his own words. "In such cases," he says, "the phlebitis may have no intrinsic characters by which to distinguish it; yet, not rarely, it has peculiar marks, especially in its symmetry, apparent metastases, and frequent recurrences. Gouty phlebitis is far more frequent in the lower limbs than in any other part; but it not limited to the limb that is, or has been, the seat of ordinary gout. It affects the superficial rather than the deep veins, and oftener occurs in patches, affecting (for example) on one day a short piece of a saphenous vein, and on the next day another separate piece of the same, or a corresponding piece of the opposite vein, or of a femoral vein. It shows herein an evident disposition towards being metastatic, and symmetrical; characters which, I may remark, by the way, are strongly in favor of the belief that the essential and primary disease is not a coagulation of the blood, but an inflammation of portions of the venous walls. The inflamed portions of vein usually feel hard, or very firm; they are painful, aching, and very tender to the touch; such pain, indeed, often precedes the clearer signs of the phlebitis, and not rarely begins suddenly. The integuments over the affected veins, (where they are superficial), are slightly thickened, and often marked with a dusky reddish flush. When superficial veins alone

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are affected there may be little oedema; but when venous trunks, as the femoral, the whole limb assumes the characteristics of complete venous obstruction. It becomes big, clumsy, featureless, heavy and stiff; its skin is cool and may be pale, but more often it has a partial, slightly livid tint, with mottling from small cutaneous veins visibly distended. The limb thus enlarged feels oedematous all through; but firm, and tight-skinned, not yielding easily to pressure, and not pitting very deeply. By this state almost alone the disease must sometimes be recognized, for it may be very marked when only a small portion of vein is affected, and that (as the lower part of the popliteal) so deeply affected as to be scarcely felt."

Schwarz has reported two cases of migrating phlebitis affecting the veins of the upper extremities that occurred in advanced cases of pulmonary tuberculosis. Neisser under the title of "*Ueber wandernde Phlebitis,*" has reported one case of his own, and collected six others from the literature in which syphilis was apparently the etiological factor. In his cases the upper extremities were most frequently affected. The lesions were examined microscopically. Recently Herrick has reported a typical example of phlebitis migrans occurring in a woman, aged 60, who had a mild osteoarthritis. The pathological condition in the case extended over a period of six and one-half months and there were twelve inflammatory lesions involving the superficial veins of the lower extremities and the epigastrium. Each process was preceded by pain in the affected region lasting from 24 to 48 hours, this pain not always being localized exactly to the site of the new lesion. The lesion itself was a superficial, red, hot, indurated area, continuous with the small superficial veins, which were at times more prominent than usual. The size of these areas was variable; the usual width being about three-quarters of an inch, the length varying from one to four inches. About these areas in some cases there was very slight local edema. There was never any evidence of serious interference with the circulation. There were no systemic symptoms.

The case I wish to report is that of a lawyer, aged 40, who complained of swelling in his right leg, which was painful at times and had troubled him for five months. His family history threw no light on the case. He was a man of good habits and had never had any venereal disease. In the fall of 1896 he had a severe attack of iritis, which lasted practically all of that winter, and which yielded finally to the administration of salicylates. At about this time he began to have attacks of herpetic stomatitis, which had affected him almost permanently since that time. From this condition he had never found any relief until the summer of 1910, when traveling in France he was given a mouth wash which contained salol. This never seemed to prevent the onset of the attacks of stomatitis but did seem to check its spread, thus greatly relieving the discomfort. His attacks of iritis have recurred at intervals of about two years, the last attack being in October and November, 1909. In 1906 he had an attack of acute articular rheumatism involving the larger joints of both extremities. He has at times had some pain and swelling of the second joint of the great toe of the right foot, which was probably a gouty manifestation.

The first manifestation of his present trouble came in August, 1910, when in London, England, the calf of his right leg became swollen and painful. The swelling remained but the pain disappeared in the course of three or four days. In November, 1910, while playing golf, he was seized with a severe pain in the lower part of the abdomen on the right side. From this time until February 14th, when I saw him first, he had some swelling of the right leg below the knee. He was able to attend to his business but he had had considerable discomfort in his right leg. Physical examination at that time revealed nothing of importance except the moderate edema of the right leg below the knee, and the presence on both lower extremities, on the extensor surfaces below the knee of several bluish-red, raised nodules, varying from two to four centimeters in diameter, which were considered to be typical lesions of erythema nodosum. Three days later an acute painful swelling appeared on the right calf. This swelling was about five centimeters in diameter, the longest diameter being vertical. He felt perfectly well and had no systemic disturbance, except a slight rise in temperature, ranging from 99 to 101 degrees. There was no swelling of any of his joints. Complete rest in bed was advised, the right leg elevated and fifteen drops of the oil of wintergreen, together with thirty grains of sodium bicarbonate were given every four hours. On February 26th, a painful rounded swelling could be felt in the calf of the left leg, and there was considerable edema of the left foot and ankle. This was undoubtedly due to a phlebitis of one of the deeper veins of the calf.

On the fourth of March the patient felt some pain in the left groin and this was associated with tenderness and swelling extending four inches below Poupart's ligament, along the line of the femoral vein. The swelling of his left leg extended from the foot above the knee, and there was a small amount of effusion into the knee joint. The swelling of the left foot was so great that the bony outlines were obliterated and the circumference of the calf was increased from fourteen to sixteen and one-half inches. The edema remained about the same for one week and then began gradually to disappear. On the 29th of March he felt acute pain in his right groin, with tenderness, and a linear swelling appeared along the line of the femoral vein, and the right leg became markedly swollen, the calf measuring seventeen inches. There was also a tense brawny edema on the outer and upper part of the right thigh. By this time the left leg had reached its normal size and the right leg remained very much swollen for about a week. Then the swelling began to disappear so that it reached its normal size about three weeks after the onset of the phlebitis in the right femoral vein. During all this time the erythema nodosum persisted, new lesions coming out in crops, and he suffered more or less from his stomatitis. His temperature varied from 100 degrees in the morning to 102 degrees in the evening. His appetitie was good and except for the discomfort in his legs the patient was in good condition. About the first of April the veins on the surface of the abdomen began to enlarge, the distension of the veins being much more marked when the patient was in a sitting position. He complained of no abdominal tenderness but, nevertheless, we considered that there had been some obstruction of the veins within the abdomen. At the same time there appeared on the left side of the abdomen, just above the crest of the ilium, a tender swollen nodule, due to a phlebitis of one of the superficial veins of the abdomen. Blood cultures were taken on two separate occasions from the median basilic vein of the right arm by Doctor L. W. Ladd, but with negative results. The blood showed nothing abnormal, except a slight leucocytosis, the count being 12,000. On the second of April, Doctor Ladd took cultures from the unbroken vesicles in the mouth, sterilizing the surface with lysol, and obtained a diplococcus, which was very difficult to grow on the various culture media. However, he succeeded in obtaining a vaccine and on the seventh of April the patient was given an injection of 12,000,000 organisms into the subcutaneous tissue of the left arm. On the following day there was a severe local reaction at the site of the injection, his temperature rose two degrees and he felt quite ill. During the next week there was a slight drop in temperature, his highest afternoon temperature being 100 degrees. On April 16th Doctor Ladd gave him a second injection of 6,000,000 organisms, which was followed next day by a sharp rise in temperature to 105 degrees, severe pain in the left axilla associated with a pleural friction rub, shortness of breath, and a pulse rate of 140. The symptoms were very alarming and a hypodermic of morphin was necessary to relieve pain. A second hypodermic was given six hours later and he passed a comfortable night. Next morning a small area of consolidation could be made out in the left lung, just below the angle of the scapula. His temperature kept up for another 24 hours, then fell suddenly to normal, the drop being associated with profuse sweating. The signs of consolidation in his lung disappeared entirely in two or three days. After the first injection of vaccine the vesicles in his mouth disappeared, and there has been no return of these or of his phlebitis during the succeeding nine months. On May 15th he was allowed to sit up in a chair, and one week later he walked a few steps. The lesions of erythema nodosum persisted until the first week in May. The conditions of his legs gradually improved; at times there would be considerable swelling if he walked too much, but on the 27th of August he was able to play golf two and a half hours without any heaviness and discomfort, although he occasionally has some swelling in his right foot and angle. At the present time he is in good health, but the veins on the surface of the abdomen are still somewhat distended, showing that there must have been considerable obstruction of the intra-abdominal circulation.

The point of interest in this case was the occurrence of phlebitis in so many different veins in a patient of rheumatic or possibly gouty tendency without much constitutional disturbance, and the subsiding of the phlebitis after the administration of the vaccine. It is impossible to say whether this was a coincidence or not, and yet it is very significant that the herpetic eruption in his mouth, from which he had never been entirely free for a period of fourteen years, disappeared after the first injection of vaccine and has not since returned.

In many of the cases recorded the inflammatory process seems to have been confined to the walls of the veins without much obstruction of their lumen, but in the present instance there must have been considerable obstruction to the flow of blood in the veins, as indicated by the extensive edema, and the distension of the veins showing an attempt at collateral circulation.

Instances of recurring thrombo-phlebitis have been recorded where heredity seemed to play an important part. The most notable of these is the case reported by Wilder Tileston. This patient, a man of 35 years, had during a period of 16 years, eight attacks of thrombo-phlebitis in the lower extremities. Of 16 adult individuals, among this gentleman's ancestors and collateral relatives, eight have shown a marked susceptibility to venous disease in different forms.

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# THE TREATMENT OF CONGENITAL DISLOCATION OF THE HIP WITHOUT PLASTER OF PARIS

## A Simple Retentive Apparatus[1]

By HENRY O. FEISS, M. D., Cleveland, Ohio
From the Surgical Service, Lakeside Hospital

THE disadvantages of plaster of Paris in the treatment of congenital dislocation of the hip are so apparent that they require almost no demonstration. In the first place, there is danger of the hip slipping out during the actual application of the plaster. In the second place, it takes considerable time to apply a plaster dressing, thus prolonging the period of anæsthesia. In the third place, even if the hip is properly put up in plaster, the soft padding which it is necessary to place next to the skin gradually becomes compressed and fixation is in part lost, so that the hip may move and slip out. Fourthly, it is difficult to obtain a good X-ray through the plaster if the plaster is very thick. In the fifth place, pressure sores which are invisible are liable to form. In the sixth place, the dressing becomes badly soiled and the patient's legs and pelvis become covered with filth and coagulated urine, causing itching of the skin which cannot be ameliorated. Finally, and perhaps most important of all, the plaster is liable to get wet and soft or to break by accident, so that in any case it loses its form, therefore no longer holding the hip in position. These seven reasons may be summed up in the statement that the plaster is unhygienic and mechanically unreliable. For these reasons it is extremely desirable to use a substitute for this kind of a dressing, and the aim of this paper is to describe such a substitute.

In contemplating something which would be better for the retention of a reduced hip, there are, generally speaking, three essential things which must be considered — these are efficiency, cheapness, and simplicity. Mechanically, the important consideration is the position of the femur in relation to the pelvis. The point here is that the femur must be maintained in the position of greatest stability. Some men have asserted that another mechanical consideration is the necessity of actually pressing the femur into the joint. This, however, is a far-fetched claim, as no pressure which is important can be applied. In most cases that angle of stability is what is spoken of as right angle abduction. It may be wise (as shown by Bradford) to put up the hip in a position of external rotation besides that of right angle abduction. This is obtained by letting the child rest on a board and letting the lower leg hang over the side of the board. At any rate, the retentive apparatus must have as its first aim this mechanical requirement, namely, the maintenance of the angle desirable in the individual case. So with this mechanical consideration before us and bearing in mind the general considerations spoken of above, we offer the description of the following brace.[1]

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[1] Dr. G. G. Davis of Philadelphia and others have reported apparatus to be used during the convalescence, after using plaster at the start. However, the present apparatus is prepared before the operation, so that it can be applied immediately after reduction, thus doing away with plaster entirely.

The apparatus (Fig. 1) consists of an iron pelvic band running about the pelvis to just beyond the anterior superior spines, to which band is fastened an iron strip running down the external aspect of the thigh, not quite as far as the external condyle. To this there are fastened two bands, one for the lower part and the other for the upper part of the thigh. The stock used is sheet wrought iron, not tempered, and ranges from 18 to 15 gage, depending on the size of the child. The width of the various bands also depends on the size of the child, beginning with $\frac{5}{8}$ of an inch for an infant. The pelvic band may be made a little broader than the others.

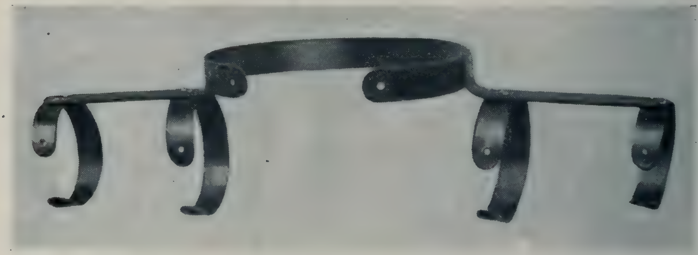

Fig. 1. Brace ready to be covered — double case.

The brace is prepared a day or two before the operation. The following measurements are made: First, the thigh is put up in a position of right angle abduction which is usually the desirable angle, then the pelvic and the two thigh measurements are made. These three bands are now prepared, the thigh bands being long enough to hold the part, going a little more than two-thirds around. The lateral strip is bent to the desired angle, so that the angle comes just below the pelvic band, and allowance is made in its length for the increased length of the thigh after the reduction, taking care however that the lower thigh band comes somewhat above the popliteal space, so as not to cut the hamstring tendons. The various bands are now tried on and their positions marked on the lateral strip, then the pieces are riveted together, two rivets being used at each junction. The position of the lateral strip on the pelvic band is half the vertical height of the pelvic band as the child lies horizontal. The brace is finished as follows (Fig. 2), rather a liberal amount of sheet wadding or light felt is wound about the whole thing, and over this either flannellet or lint is wound and fastened with a few stitches. One end of each band is provided with a webbing strap which can be fastened to the opposite

[1] The author wishes to express his appreciation of the valuable help offered by Mr. George Gilford of the Lakeside Hospital Brace Shop, in the construction of this brace.

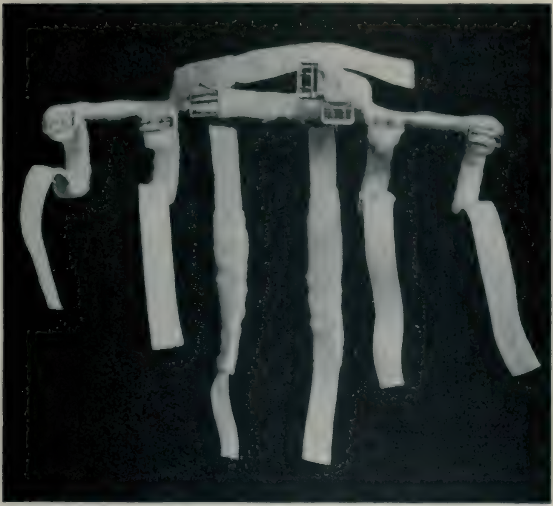

Fig. 2. Same brace finished.

end by means of a buckle, thus enclosing the part. In addition two peroneal straps are fastened to the pelvic band. The brace is put on by springing the bands apart a little, like a Thomas hip brace, and applied next to the skin (Fig. 3). In double cases, both sides are made symmetrical.

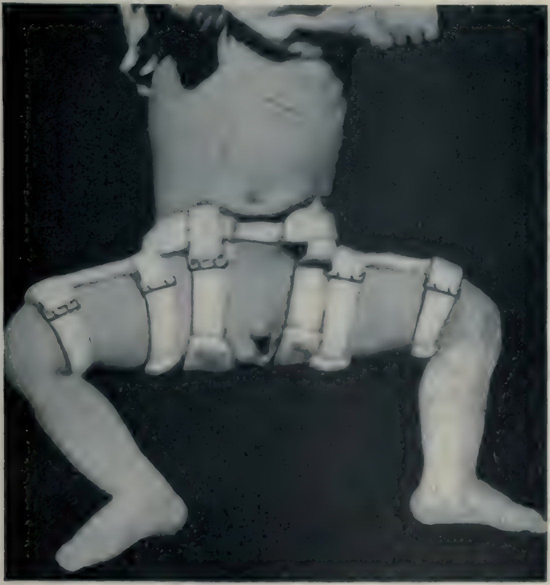

Fig. 3. Same brace applied.

If, after reduction, some other angle is desirable than that of right angle abduction, the brace is very easily altered on the spot by bending or twisting, because the metal is untempered. If it is put up in Bradford's position, the brace will hold just as it is. The whole apparatus can be made very quickly and the cost of it in Lakeside Hospital Brace Shop is from two to three dollars, depending on whether it is a single or a double case.

During the convalescence the angle of the femur to the pelvis is gradually changed. This can be done without removing the brace, but it is wiser to remove it and rewind it with fresh wadding and lint at such periods, and when this is done the brace is as good as new, so that there is practically no additional cost after the brace is once applied.

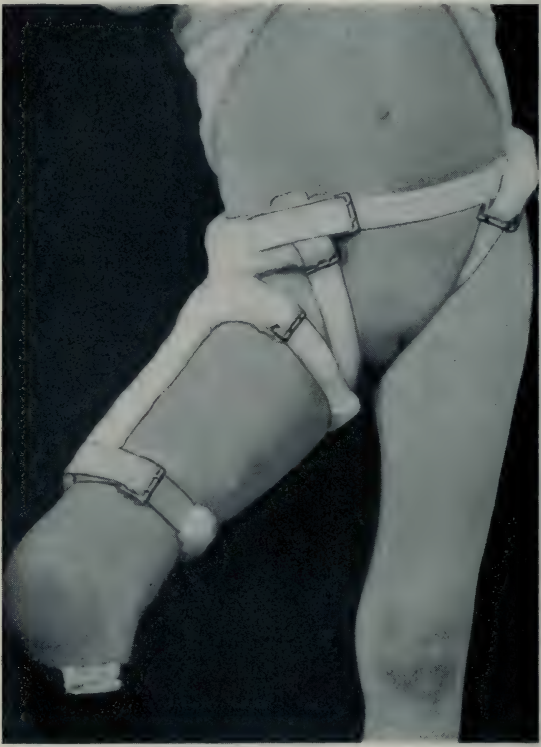

Fig. 4. Patient wearing single brace — front view.

Besides fulfilling the essential requirements of cheapness, simplicity, and efficiency as above apparent, the brace has other important advantages which the plaster of Paris dressing does not offer. For one thing the brace is ready immediately after reduction and is applied in a moment. A good X-ray can therefore be obtained immediately after the reduction to show whether the hip is in place, the child being still under the influence of the anæsthetic. Even without the X-ray one can know pretty well whether the hip is in because even with the brace on, one can palpate the parts and make his measurements. Again, if there is any pressure the brace is very easily adjusted by springing it a little here and there, or by twisting any of the bands. If at any time during convalescence it is desirable to change the angle, this can be done very easily as suggested above. (Figs. 4 and 5 illustrate a patient eight years old, two months after reduction; the angle of the thigh to the pelvis has been gradually changed from a right angle to the present dimension.) This adjustability is of the greatest importance. Again the brace is very light, thus making it very easy for the child to get about with the brace on. In short, the brace has none of the disadvantages which plaster of Paris has, and from both the hygienic and the mechanical point of view answers every reasonable purpose. The advantages can best be appreciated by trying the brace for oneself.

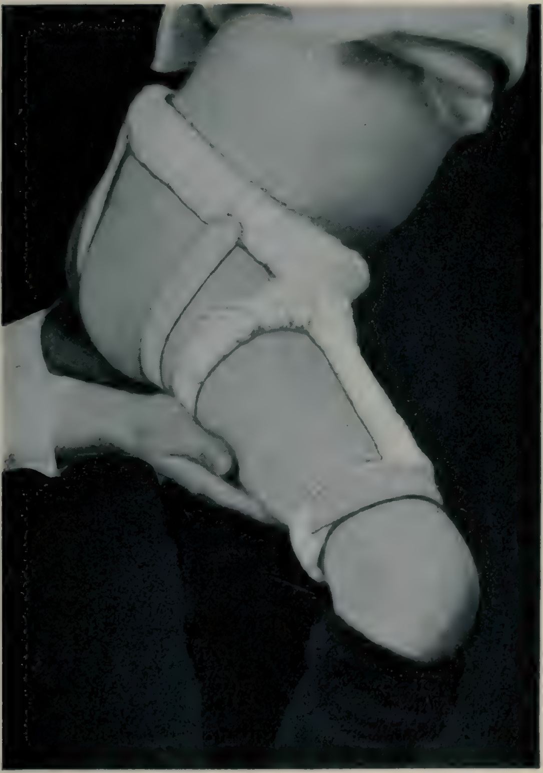

Fig. 5. Patient wearing single brace — side view.

We have nine cases on record[1] which have been held by this method,[2] and although this number is very small, the advantages have been so manifest in these few cases that we feel reasonably certain that we will continue using it in future. One case in special is of considerable significance and is, we believe, the youngest case that has ever been held. This case was that of an infant less than a year old. It was noted to have its hip out of place and contrary to the ordinary indications it was deemed wise to attempt to reduce this hip. This reduction was easily accomplished under ether and a plaster was applied. A few days later the plaster was found soft and not holding and an X-ray showed that the hip was out. Another manipulation was attempted, another plaster was applied but once again the plaster got softened by urine and the hip slipped out. It was at this time that the brace above described was first used. Both hips were put up in order to get greater stability. An X-ray was taken immediately after reduction, another (Fig. 6) two months later, with the brace on, and another four months later, after the apparatus had been discarded. All showed the hip in place.

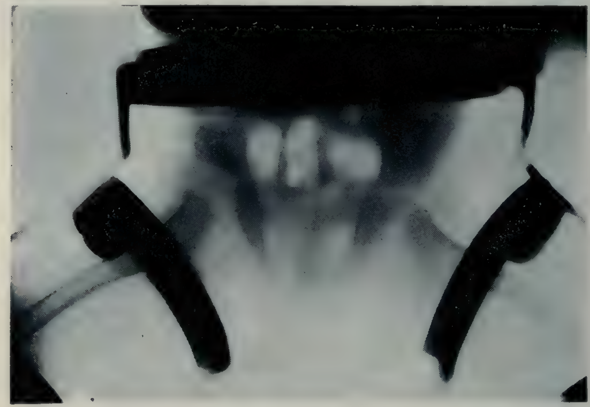

Fig. 6. X-ray of infant mentioned in the text, two months after reduction, still wearing the brace. Note symmetry of joints, suggesting advantage of early reduction, thus made possible by brace.

The deduction from this example is very important, it means that we can reduce congenital dislocated hips even in infancy, whereas before, we had been taught that it was wiser to wait until the child was old enough to keep itself clean and dry. Of course, if we can put these hips in in infancy or early childhood, it means that the prognosis for these cases is better than if we have to treat them at a more advanced age, because it is indisputable that the older the child, the more perverted the bones and soft parts become in their development.

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[1] For the privilege of working on all but one of these cases, I am indebted to Dr. Dudley P. Allen, chief of surgical service at Lakeside Hospital.

[2] In a tenth case a slough was produced by the brace, and it had to be removed. It was later discovered that the brace was padded accidentally with only one layer of sheet wadding, thus explaining the undue pressure.

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# THE ADVANTAGES OF BRACES OVER PLASTER JACKETS IN POTT'S DISEASE.*

BY HENRY O. FEISS, M. D., CLEVELAND, O.

It is no longer stylish, at least so far as medicine is concerned, to quote the words of men who have made it their life study to learn to think, but in the present instance I cannot refrain from repeating the poignant words of Locke who says,† "I cannot but own, that men's sticking to their past judgment and adhering firmly to conclusions formerly made is often the cause of great obstinacy in error and mistake. But the fault is not that they rely on their memories for what they have before well judged, but because they judged before they had well examined. May we not find a great number (not to say the greatest part) of men that think they have formed right judgments of several matters, and that for no other reason, but because they never thought otherwise." I use these words apropos of the theme which I have chosen for my paper to-day. The subject of this paper has to do with the extensive use of plaster jackets to-day, a method of treatment which, it seems to me, is somewhat crude for the present era, and which is perhaps more the result of custom, habit, and training than the result of intelligent thought given to that subject in its modern aspect, for as Locke continues, "Men often imagine themselves to have judged right only because they have never questioned or examined their own opinions."

Although plaster-of-Paris has been used in surgery for a great many years, the use of plaster jackets for affections of the trunk became popularized when the elder Sayre first applied them in cases of lateral curvature. That this method of treatment was relatively an important one for that time there can be little question, for jackets came to be used also in cases of Pott's disease and the improvement obtained in many of these cases showed that an advance had been made. With regard to lateral curvature, however, the success was not what had been expected, and although plaster-of-Paris is still frequently used for such cases, that disease must still be classed as an incurable affection, whether treated by plaster-of-Paris or by other means. But this was not so in cases of Pott's disease, the improvement here having been distinct, although not always marked.

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* Read before the American Orthopedic Association at its Twenty-fourth Annual Meeting, held at Washington, May 3–5, 1910.

† Essay on the Human Understanding.

As time went on plaster jackets came to be used more and more commonly, especially in Germany and America; and to-day the weight of opinion is that, other things being equal, the plaster is the more scientific and preferable method of treatment, braces being used only in convalescent stages and only in such cases where plaster jackets could not otherwise be applied.

As intimated above, my object to-day is to weigh the evidence for and against plaster jackets and to suggest that perhaps the pendulum has swung too far and that both from the hygienic and mechanical points of view, plaster jackets are not as efficient a means of treatment as braces.

The object of plaster-of-Paris jackets in diseases of the spine is said to be fourfold: 1, to fix; 2, to protect; 3, to support and 4, to correct. Some men have asserted that plaster jackets can even extend the spine. On theoretical grounds this is possible, but practically, it is never done. If there is any extension possible in the spine at all, it has to be sufficient to counteract and go beyond the actual superincumbent weight above the seat of the lesion. No argument is necessary to prove such a thing as practically impossible. If it were possible, it would imply that the body were taken hold of above the lesion in such a way that the column is actually pushed up and this must mean not a grasp of the shoulders, because that has nothing to do with the column; nor of the chin, because if that is grasped it implies locking of the jaw; but a hold on the occiput and forehead. This is difficult, to say the least, because these parts of the skull offer no favorable place for grasping. I think it is safe to say that extension is never gained by means of a plaster jacket.

With regard to fixation, the amount gained is relative only, because in order to make a plaster jacket bearable, it has to be padded to keep the plaster from touching the skin directly. Therefore, the padding must be somewhat soft and must give. The result is that after a jacket has been applied and fits finely, the soft padding gradually compresses and this compression must mean that a space comes to exist between the plaster wall and the wall of the body. Moreover, a jacket goes around the chest and therefore must be roomy enough for the maximum expansion in inspiration, so that during expiration the jacket is looser. In addition to these two points, we have the atrophy of the muscles under the plaster. This also increases the space between the plaster and the body. For these three reasons perfect fixation cannot be obtained by means of a plaster jacket.

With regard to protection and support, the two words have mechanically the same significance, for the more support obtained the more protection there is to the lesion. But what is more essential is the fact that the support also diminishes in direct ratio to the amount of fixation that is lost as the jacket is worn. There is, moreover, one mechanical detail, on account of which the support is very much weakened in a jacket when it is entirely new, and that is the window which it is usually necessary to cut out over the kyphos. If this window is not cut, there is danger of a slough over the knuckle, and if it is cut, the main fulcrum of leverage for support as well as for correction is lost. The kyphos protrudes through the window and the resistance which ought to be brought to bear on the transverse processes in that region is not present. To counteract this loss of resistance in plaster jackets, Calot, as is well known, has stuffed padding through the window, repeating this at short intervals, hoping to gradually get enough pressure so that the leverage would be applicable on the transverse processes. It is very doubtful whether he gains much by this method.

With regard to the correction of the deformity this also loses its value in direct proportion to the loss of fixation. Our opponents will state that even if the above arguments are correct, facts show that the patients do gradually get corrected in plaster jackets. This I admit, but the correction is not on account of the actual force brought to bear by the plaster jacket but simply in its preventing the patient from getting worse. The fixation gained by the plaster jacket, although not complete, is sufficient for that purpose, and as the natural tendency of the child is to grow in height and as the shell of plaster prevents his weight from collapsing forward more than a certain amount, there is often a relative improvement in the deformity, but that a true correction of the deformity takes place has, so far as I know, never been definitely shown.

Besides these important mechanical disadvantages there are certain others which ought to be mentioned. A plaster jacket after it is applied must be kept dry. If a patient sweats or gets wet by accident, the jacket is spoilt. Moreover, the plaster jacket after it is put on cannot be removed for a bath. Therefore, it is a fit breeding place for all kinds of parasites of the skin, such as lice, fleas, and even bedbugs.

Again, a plaster jacket if it answers the purpose for which it was put on, must not come back broken. A large number of plaster jackets that I have seen put on both in European and American clinics, have come back with their fronts cracked or soft, so that the pelvic fixation was lost, and this in spite of the fact that they were put on with the greatest care, with the best skill that could be mustered and as thick as the patient could reasonably stand.

Even this is not all. The plaster jacket conceals what is going on both in the chest and in the belly, preventing the examination of the surface of the skin, as well as the vital organs themselves. If a slough or an abscess is forming, it cannot be seen. If one of the exanthemata breaks out it may not be discovered, and scarlet fever, as is well known, usually begins on the chest. If typhoid fever, pneumonia, or any other disease is suspected, the jacket must be removed for proper study of the patient, and yet one hesitates before removing a jacket even for such suspicions as these, as it is not always expedient to reapply the split plaster or make a new one. For all these reasons and perhaps others, I state that plaster jackets offer certain distinct mechanical and hygienic disadvantages which can be overcome by means of the other mechanical methods of treatment, and I refer more especially to the use of braces.

When I speak of braces, I have in mind such a simple contrivance as the Taylor back brace or one of its modifications. The principle of this brace is simply a posterior double upright fitted accurately to the transverse processes of the spine running well above the lesion with a little more pressure next to the knuckle, and fastened to the trunk by means of a light apron which is held down by means of peroneal straps. The head support, if one is necessary, must enclose the occiput and forehead. The whole apparatus must be light, carefully made, and accurately adjusted. I do not wish in this present discussion to go into the details of construction of such a brace, as every orthopedic surgeon uses one of that general design. Suffice it to say, that if the brace fulfils the requirements above mentioned, it will, I believe, be a better mechanical and hygienic contrivance for the ambulatory treatment of Pott's disease than a plaster jacket for the following reasons:

In the first place with regard to fixation, such a brace does everything that the jacket does and more, because if atrophy takes place in the muscles or if some of the pressure is lost as the spinal pads compress, the straps on the brace are simply made a little tighter and so readjusted once or twice a day, always keeping the brace firmly fastened to the body. With regard to breathing, the steels have sufficient elasticity to give as the patient inspires and yet do not lose their fit when the chest is contracted. Therefore, a brace must fulfil the requirements of support and protection, because fixation is not only obtained, but actually maintained.

Again the pressure comes directly over the transverse processes next to the disease and so the fulcrum for leverage for the sake of support and correction is always present. This is proven by the fact that in every well fitted brace, pressure marks develop next to the knuckle, showing that the stresses at this point are really effective.

Moreover, there is little danger of serious loss of adjustment or breakage in a well constructed brace. It is lighter than a plaster jacket and a great deal cooler. It conceals nothing. Sloughs do not form. Abscesses and diseases of the skin and viscera can be watched for, and if care is used the patient can be bathed. I believe that any orthopedic surgeon, if he examines his own experience with sincerity and reason, must admit that if he has a brace-maker who has any skill at all, he can accomplish more with a brace than with a plaster jacket.

Strange to say, the chief argument that one hears against the use of braces, and in favor of plaster jackets, is that the mother of the patient cannot remove the jacket. I believe that this is an argument so trivial that it may almost be thrown out of consideration. In the first place, the parents of the patient could easily remove the plaster jacket if they wished to do so. All they have to do is to soften it with water and cut it down. In the second place, the temptation to remove a plaster jacket is far greater than one to remove a brace on account of the filth alone. But even if the temptation to remove a brace were greater, this argument from a professional and scientific standpoint can have no force, because we are not considering temptations but efficiency. If a brace happens to be a more efficient instrument it should be used whether or not it can be more easily removed, and certainly the fact that it can be more easily removed seems to be an argument in its favor, as I have shown.

With regard to another argument that is often heard against the use of braces; namely, that the mother will not keep the brace accurately adjusted, that is not so. I have always noted that the poor mothers in the clinic take far more interest in their children than the average nurse of a rich man's child, because a nurse is often thinking of other things and the mother is thinking of her child. It is merely necessary to teach the mother how to apply the brace and to keep it adjusted. Of course, if the machine is very complicated and she is not taught properly, there may be loss of adjustment, but if the brace is simple and a little care is taken in showing her how to use it, she never forgets her lesson.

But the greatest advantage of a brace over a plaster jacket is the fact that one can control the stresses which are brought about. A brace can be made to do certain things and after it is once applied so as to do these things, other things being equal, it may be relied upon.

To sum up, therefore, I say that a brace fixes, supports, protects, and corrects with all the efficiency of a plaster jacket, and more, because it maintains the mechanical requirements as long as desired. And as it is lighter, cooler, cleaner, more comfortable, and from every other point of view more scientific, I believe it is the preferable method of treatment.

Not long ago, there was brought to Lakeside Hospital a boy about six years old, wearing a plaster jacket. It had been applied in one of the best dispensaries in New York City. It enclosed the trunk from the pelvis up and then went under the chin and around the occiput and forehead. The padding was smooth, the plaster was not broken. It was prettily molded around the pelvis and head and would ordinarily be styled a fine piece of work. And so it was. I examined the boy carefully before taking off the jacket, which had been on about two months, and found that he could move his head just as easily in the jacket as I could move my own, because the padding had become compressed and allowed plenty of space about the head. I had the jacket removed, and when it was opened up I found it literally alive with a whole menagerie of diminutive beasts which seemed to be thriving and living happily on the afflicted boy. As soon as the jacket was removed, the little youngster started to scratch his head with both hands, but he didn't scratch long on his head because he was anxious to scratch his neck and then he had to stop that because he had to scratch the rest of his body. He was the most uncomfortable little creature that I had seen for some time. I examined his back and I found that a knuckle was present in the neck. The mother stated that this was no better, and, perhaps, a little worse than when she had last seen it. She maintained that the child had been under treatment ever since the onset and that the treatment had not had the slightest effect on the deformity. We put the child in bed on a frame and it took about two weeks to heal the skin and get rid of the vermin. We next put on a light brace with a head support. He is wearing this brace yet and is doing well. His deformity is not getting worse, the skin is clean, the mother keeps the brace nicely adjusted, and the muscles in the trunk are developing to a reasonable degree.

So with dozens of other cases which I have seen in this country and abroad; the removal of the jacket showed a mass of filth, vermin, and sloughs, which was disgusting.

Therefore, I am slowly endeavoring to give up the use of plaster jackets as much as possible. There are certain cases where they may be useful. Perhaps, in an adult where only one or two jackets are indicated and perhaps, in certain emergency cases in the acute stage. Outside of these, I seldom order a plaster jacket to be applied. I advise the patient to be placed on a frame* and follow that up with a brace which I know fits. If there is an acute exacerbation in the disease I do not change to the jacket, but I put the patient back to bed with his brace on. In this way I believe I have accomplished certainly as much if not more than those who use plaster jackets.

With regard to the use of plaster of Paris in other parts of the body, my rule is to use braces whenever it is feasible to do so. I expect to have more to say on this score in other reports, but there is no comparing plaster jackets with plasters which enclose the limbs, because in the latter cases the skin is much less irritable, fixation is much more easily obtained on account of the shape of the parts, atrophy is a much less important factor, and there are no vital organs enclosed.

In conclusion, I therefore state more with a sense of prognostication than with even a desire for suggestion that the use of plaster jackets in this mechanical age will, I believe, soon be a relic of a cruder era, and that the use of braces, as constructed now-a-days, will mark the beginning of refinement in protective apparatus.

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* A frame for this special purpose will be described in a later report.

No. 12

# FIBROMA OF THE NASO-PHARYNX WITH REPORT OF FOUR CASES.

By WM. B. CHAMBERLIN, M. D., of Cleveland, O.

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True fibromata of the naso-pharynx are rare tumors, few such cases as a rule falling to the lot of any one operator. Ingals, of this society, in a rather careful review of the literature, has reported more cases than any other single observer.

These tumors have their origin from the dense fibrous tissue covering the basilar process of the occiput, the middle lacerated foramen, the under surface of the sphenoid, the first cervical vertebra and the spheno-palatine fossa. Escat of Toulouse, however, agrees with the view of Jacques that the origin of all such tumors is primarily nasal, the most frequent site being the articulation of the vomer with the sphenoid and that the involvement of the naso-pharynx is in all cases secondary. He considers the contrary view as due to the fact that the cases as a rule are seen late in the disease or on the post mortem table, when the primary focus can no longer be made out. This view is not held by other observers.

They are hard, dense tumors, richly supplied with blood vessels and possessing a decided tendency toward rapid growth. Extension is usually in the line of least resistance, though they do not hesitate to invade or erode any tissue, however dense, which may interfere with their growth. The soft tissues of the neck and face, as well as the nose and its accessory sinuses, are frequently involved; while the growth, if unchecked, ultimately invades the skull cavity itself. These tumors are non-malignant in that they do not form metastases. From their location and because they so frequently invade important structures they are exceedingly dangerous to life and demand destruction or removal. The base of attachment is always broad, though the tendency to form adhesions makes it difficult at times to distinguish where the origin really is. The nourishment, however, is always from the point of original growth and attachment. Frequent and severe hemorrhages are common.

According to Zarniko, naso-pharyngeal fibromata consist histologically of dense fibrous tissue with elastic fibres intermingled. Although cells are as a rule scarce, there are frequent nests of new formed fibrous tissue rich in cells. The differentiation from fibro sarcoma is frequently difficult. Blood vessels are frequent and often of great size. This description coincides with the histological findings in the four cases presented.

A striking peculiarity is the fact that the overwhelming majority of those afflicted are males, and between the ages of 10 and 25 years. After the age of 22 or 25 these tumors tend to spontaneously disappear, so that this period is spoken of as the age of immunity.

It is rare that a surgeon has the opportunity of seeing these cases in their incipiency, as medical aid is not summoned until more or less distressing symptoms arise. Among the earliest symptoms may be mentioned nasal obstruction and the resulting voice peculiar to it. The anaemia is striking, if bleeding has been frequent. As a result of the obstruction the nose is filled with secretion which is often of foul odor. Dyspnoea, dysphagia and deformities of the nose or face belong to the later developments of the growth; while neuralgias may result from pressure on the branches of the trifacial nerve. Involvement of the middle ear is not uncommon. Death results from the anaemia, due to frequent hemorrhages or from meningitis, as the result of the extension into the skull cavity.

The diagnosis in advanced cases is usually easy, from the appearance of the patient. On examination of the nose nothing is at first seen but thick muco-purulent secretion. If the growth is small, one side of the nose may still be free. On removal of the secretion one observes a pale red or pink tumor, very resistant to the probe and often bleeding easily on slightest manipulation. Examination may even give rise to a severe hemorrhage. On looking into the mouth the growth, if large, can be seen pushing the soft palate forward and extending downward well into the pharynx. Smaller growths are recognized with the post nasal mirror, while their consistency may be determined by digital examination. The exact point and extent of the attachment can in most cases scarcely be determined. As a rule, only the under surface of the tumor can be seen with the mirror, while the growth fills the space so completely that palpation gives little further information.

Fibromata of the naso-pharynx must be differentiated, in the first place, from pseudo naso-pharyngeal polypi. These are the ordinary mucous polypi, so frequently met with in the nose, which have slipped back into the naso pharynx and found there greater room for development. An intermediate stage between the mucous polyp and the true naso-pharyngeal fibroma is the fibrous polyp which springs from the margins of the choanae and the tissues immediately adjacent thereto. In consistency, as well as on histological examination, it closely resembles the true fibroma. In practically all the reported cases this differentiation from the fibrous polyp is not clear, all fibrous tumors of the naso-pharynx being classified in one group, whether they be sessile and arise from the naso-pharynx proper, or pedunculated and have their origin from the posterior boundaries of the nasal cavities. This differentiation, however, seems logical in that the prognosis, as well as the operative procedure, varies decidedly with the character of the tumor. Zarniko calls attention to the following points in the differential diagnosis:

(1) The pseudo as well as the fibrous polyp, is always pedunculated, the pedicle usually small—the true fibroma almost never.

(2) The latter bleeds easily and spontaneously—the former never.

(3) The tendency to rapid growth and erosion of neighboring structures is far greater with the true fibroma than with the mucous or fibrous polyp.

The differential diagnosis from sarcoma presents greater difficulties. Both bleed readily, and both involve neighboring structures; sarcoma by extension, fibroma from pressure. Microscopical examination of excised portions must here be resorted to. Fibromata, too, give no glandular involvement, while the enlargement of the cervical glands in sarcoma may be a striking feature. The histological examination of an excised gland in doubtful cases may serve to clear the diagnosis.

As before mentioned these tumors, while non-malignant in the restricted sense, are exceedingly dangerous to life and demand destruction or removal on account of their location and their tendency to invade important structures by pressure. Lincoln in his exhaustive article published in 1883 well summarizes the objects of treatment as:

(1) The removal of all growths, as far as possible, together with destruction of tissue at the point of origin.

(2) The avoidance of accidents at, or immediately following the operation.

(3) The securing of the least possible external deformity.

The dangers are (1) shock at the time of operation (2) hemorrhage during the operation or immediately after. The former danger has been largely minimized or removed by improvements in technic.

Treatment is in all cases entirely surgical and may be divided into the conservative and the so called radical treatment. The former, or a modification of it, is the treatment practically universally in vogue today; while the latter was the practice of the older surgeons, especially those of England, Germany and France. We find no less an authority than Doyen, however, quoted by Delavan, asserting that "he never saw a tumor which could not be removed through the natural passages." In defense of the older surgeons it may be said that the cases seen by them were frequently more advanced, while those seen by the rhinologist today are usually in the earlier stages of growth. Dieffenbach, quoted in Koenig's surgery, in speaking of these growths says: "Great courage is required to undertake this operation, because the surgeon is almost compelled to choose between one of three conditions, (1) choking to death during the operation, (2) bleeding to death, (3) not finishing the operation." Certainly such dangers as these are largely eliminated by the technic in use at the present time.

The radical operation involved a preliminary tracheotomy with subsequent removal of the maxilla or other bones of the face. The resulting deformity was frequently frightful, while deaths on the table or shortly after were not uncommon. Above all the liability of recurrence was in no way minimized by such heroic measures. Lincoln, choosing arbitrarily the years 1867 to 1883 inclusively, could find only 58 cases reported in literature with 74 operations, three of those reported being his own. In those cases operated by removal of the bones of the face over 25% died on the table or shortly afterward. There were frequent recurrences. Delavan collected 120 cases in the years 1891 to 1901. In those cases operated by the older method there was a mortality of 25.9%, with recurrences in 15.4%. In 66 cases operated by the modern method there was not a single fatality. For this change in operative procedure, with its resulting decrease in mortality humanity is indebted in large part to modern specialism.

The modern operation consists of the removal of the growth, when possible, through the natural passages, the nose and the mouth. This procedure is successful in the vast majority of cases. Where the view is insufficient or when the accessory cavities of the nose are involved, additional space may be secured by splitting the soft palate, removing portions of the hard palate or by a Denker operation immediately preceding the removal of the tumor. Injections of monochloracetic and trichloracitic acid, as well as electrolysis and galvano cauterization have also been successful in the hands of many operators. These latter measures may also be used subsequent to the removal of the major portion of the tumor with scissors, forceps and the hot or cold snare. The inclusion of a sessile tumor within the bite of a snare is, however, a matter of extreme difficulty. It is frequently impossible. For this purpose the method and forceps suggested by Ingals are most ingenious if the hot snare is used. The forceps of Stucky, can be used with advantage when evulsion is attempted.

If one accepts the classification of Zarniko only cases 1 and 4 would belong to the true naso-pharyngeal fibromata. Cases 2 and 3 were distinctly pedunculated and would therefore belong to those classified as fibrous polypi.

Case 1. George R., age 21—farm hand, first seen in October, 1908. Complained of increasing nasal obstruction for an indefinite period. The voice was nasal in character and there was considerable loss of hearing. Examination through the nose showed on both sides a hard firm mass in the naso-pharynx, with apparently no involvement of the nasal cavity. Examination of the naso-pharynx showed a large, pale red mass practically filling the cavity. Its point of origin could not be determined. On palpation this mass was of extremely firm consistency and was not freely movable. Oct. 25. Ether anæthesia. Patient in the Trendelenburg position. Mouth held open with Whitehead gag with tongue depressor attachment. The tumor was attacked with scissors and strong post nasal forceps. A large piece was evulsed with profuse hemorrhage. This was controlled temporarily by packing, when on examination with the finger a second and larger mass was defined. The second mass was quickly evulsed in the same manner. The resulting hemorrhage was frightful, but was ultimately controlled by a post nasal tampon. The condition of the patient was now alarming, necessitating application of heat and infusion on the table. After return to the ward recovery, though slow, seemed at first uneventful. The packing was removed on the third day with no sign of hemorrhage. On the morning of Nov. 6th, twelve days after operation, the patient was up and was examined with the mirror and very carefully with the finger. There was no resulting hemorrhage. Several hours later the house surgeon was hastily summoned to the ward to find the patient almost *in extremis.* The naso-pharynx was again packed and the hemorrhage quickly controlled. The packing was removed on the third day, no hemorrhage resulting. Nine days later, or twelve days after the second hemorrhage, another severe hemorrhage occurred, making the patient's condition indeed critical. The hemorrhage was controlled by packing by Dr. Fox, the house surgeon, but two subsequent hemorrhages during the night necessitated repacking with larger tampons. The day following the right common carotid was ligated by Dr. C. A. Hamann, the naso-pharynx still being packed. Packing was removed on the third day with no further bleeding. Recovery was slow but steady and the patient was discharged Feb. 12th. He was seen by Dr. Fox in December, 1910. His health was excellent and he had gained 40 pounds in weight.

Case. 2. Boy, aged 17, complained of left nasal obstruction for past year—some deafness but no history of suppuration. On nasal examination a dense firm mass was seen blocking the left nares and encroaching somewhat upon the right. The mass was readily seen with the mirror and on palpation was firm and resistant but very freely movable. It was easily removed under ether anæsthesia by the cold wire snare—the snare being introduced through the nose. The tumor mass was distinctly pedunculated, the pedicle being small. Recovery was uneventful.

Case 3. Laborer, aged 28—complained of complete obstruction of the right nares and partial obstruction of the left for past eight months. During this period the voice had been markedly nasal in character. A snap shot diagnosis of naso-pharyngeal fibroma was made from the patient's voice and facial expression. On examination of the right nares much thick, purulent secretion was removed, after which a dense pale red tumor mass was seen projecting forward from the naso-pharynx. There was no mass visible on the left. With the post nasal mirror the growth was readily seen at about the level of the soft palate. On palpation it was hard, firm and apparently pedunculated. This case passed out of my hands and was later operated by a colleague, Dr. I. A. Tripp, to whom I am indebted for the following. Removal was accomplished by means of evulsion through the mouth, a Peters snare being used. The origin was evidently from the middle turbinal, a large portion of which was torn away with the tumor. This tumor measured 6 cm. in length by 4 cm. in diameter. Bleeding was profuse for a few minutes but soon subsided. The naso-pharynx was not packed. There has been no recurrence of the growth.

Case 4. Howard P., school boy, aged 10 years, gave a history of increasingly difficult nasal respiration for past eight months, until breathing was only possible by mouth. He was fairly well nourished, with an expression suggesting adenoids. On examination there was considerable thick mucus blocking both nostrils. On removing this and contracting the turbinals with adrenalin a firm, resisting, pale red mass was disclosed completely blocking the right nares posteriorly. There was some encroachment on the left side. With the post nasal mirror a growth was seen situated largely on the right side but extending over to the left. It was smooth in contour, non pedunculated and apparently about the size of an English walnut. Its point of attachment could not be made out. On palpation it was firm, resistant and not movable. Operation occurred on the day following. Anæsthetic and position were the same as the previous cases. Preliminary to the operation the right external carotid was uncovered and two ligatures placed around it, but not tied. The growth on account of its firm attachment could not be evulsed, but was removed piece-meal by biting forceps introduced into the naso-pharynx through the mouth as well as through the right nostril, the index finger of the left hand in the naso-pharynx serving as a guide. All growth was removed until the naso-pharynx seemed clean and free. The hemorrhage was not profuse but the naso-pharynx was packed. The ligatures on the external carotid were now removed and the wound closed, healing promptly by first intention. Unfortunately at this first operation there was considerable laceration of the soft palate necessitating repair. Packing was removed the day following. The patient left the hospital on the fourth day in good condition. On examination at the office some days later, while the naso-pharynx was fairly free, a considerable mass was made out in the right nasal fossa. Repeated operations have been performed since—September 26th, November 21st, January 28th and April 29th; when the last operation was performed. There have been occasional attacks of otitis media with spontaneous rupture of the membrana tympani. The ear is at present dry. Subsequent to the last operation the growth was cauterized through the right nasal fossa at weekly intervals. Although there was some shrinkage, these attempts were ultimately given up on account of the intractability of the patient and the increasing difficulty of producing a satisfactory anæsthesia Cauterization and electrolysis under general anæsthesia have not as yet been tried. At the last operation the erosion of the sphenoid and basilar process of the occiput seemed greater than at previous times. There was also some apprehension lest the forceps at one time had entered the skull cavity. The outcome and treatment of this case are subjects in which I wish to elicit your interest. Can the patient continue to be subjected to operations four to six times a year until spontaneous resorption occurs? A so-called radical operation is out of the question. Whether the growth could be more completely removed through the added space secured by a preliminary Denker operation and whether the patient could withstand such an operation seems doubtful.

For the histological examination on these cases I am indebted to Dr. O. T. Schultz, Asst. Prof. of Pathology in Western Reserve University. His report is as follows:

Case 1 (Roth). The stroma is very dense, due to the marked production of intercellular fibres. The stroma nuclei are narrow, compressed and widely separated. Blood vessels are numerous; most of them are thin walled and some are quite wide. The larger arteries are thick walled. In the superficial zone of the tumor the blood vessels are particularly numerous and the stroma is not so dense as in the deeper areas. The tissue immediately beneath the epithelium is rich in small lymphocytes. In the superficial portion of the tumor there are several areas of hemorrhage. The tumor shows no degenerative changes except a moderate hyalin degeneration of the thickened walls of the arteries.

Case 2 (Fuller). The stroma is more cellular than that of Case 1. Blood vessels are numerous, but thin walled, not cavernous, and not so prominent as in Case 1. Several obliterated arteries are present. The stroma nuclei are numerous, spindle shaped and vesicular. Development of intercellular fibres is less marked than in Case 1. The typical fibroma structure extends directly to the covering epithelium.

Case 3 (Bringman). The stroma is soft and fairly rich in young spindle nuclei. Intercellular fibres have been only very slightly developed, the tissue in general looking somewhat myxomatous. The tumor is well supplied with blood vessels, of which a few are wide, thin walled and cavernous; there are a few very thick walled arteries; most of the vessels are narrow and compressed, with numerous spindle nuclei just outside the endothelium. About some of the vessels lymphocytes are present in moderate numbers. The tissue shows no degenerative changes.

Case 4 (Phillips). The stroma is very dense, like that of Case 1. The narrow condensed nuclei are widely separated by well differentiated fibrous tissue. Blood vessels are numerous and fairly prominent because of the development of their walls. Some are quite wide and dilated. The artery walls are very thick and rich in nuclei. Immediately beneath the epithelium the stroma is not quite so dense as it is deeper down.

Summary: The four cases show the characteristic, typical, fibroma structure. Common to all are the cellular poverty and the predominance of intercellular substance, the absence of degenerative changes in the stroma, the richness in blood vessels and the proliferative changes in the walls of the larger arteries. Cases 1 and 4 are very much alike and show the greatest density of stroma, due to differentiation or development of intercellular fibres. Case 2 is more cellular than either of the two just mentioned; the larger number of nuclei is associated with a corresponding lack of differentiation of fibres. In Case 3, although the stroma nuclei are widely separated, the intervening tissue has undergone little differentiation and has an almost myxomatous appearance. None of the tumors is cellular enough to suggest the slightest possibility of sarcoma.

In the foregoing cases I realize that I have contributed little that is original. The use of the Whitehead gag with tongue depressor attachment and the Trendelenburg position I have not seen referred to in the literature. Both I consider a decided advantage. The Trendelenburg position furnishes an excellent survey of the field and certainly reduces to a minimum the possibility of aspirating blood into the larynx or trachea.

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# Michel's Clamps for Closing the Skin Incision

By HUNTER ROBB, M. D., Professor of Gynecology, Western Reserve
University, Cleveland.

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# Michel's Clamps for Closing the Skin Incision.

By HUNTER ROBB, M. D., Professor of Gynecology, Western Reserve University, Cleveland.

Every surgeon knows how difficult a matter it is to procure a suture material that is not only sterile to begin with but which will not itself become infected while approximating the skin surfaces. During the past three years and a half we have been using with a considerable amount of satisfaction Michel's clamps for closing the abdominal skin incision. Our experience makes us feel that in a considerable number of cases they can be substituted with advantage for the ordinary suture material for approximating the skin edges.

Some of the advantages to be derived from their use are as follows:

1. The clamps can be easily rendered sterile.
2. They are inexpensive, and can be used over and over again.
3. They are easily and quickly applied.
4. They adapt themselves to the swelling of the surrounding tissues.
5. They can be conveniently carried.

The only real disadvantage connected with their use is the slight discomfort to the patient, when they are removed from the skin. It is unnecessary to apply more than four or five of the clamps in closing the skin of the average abdominal incision. They are placed at intervals of about an inch, or a little over. The slight amount of pouting that sometimes takes place between the clamps does not seem in any way to affect the perfect healing of the wound.

Our results in the 182 cases in which we have used the clamps are, on the whole, satisfactory, but we have not employed them as yet perhaps in a sufficient number of cases from which to draw any positive conclusions, as to the frequency

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*Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, April 7, 1911.*

with which primary union of the incision takes place following their use.

## SUMMARY.

| | |
|---|---|
| Total number of cases in which clamps were used | 181 |
| Condition of incision not definitely noted in history | 37 |
| Analysis based on the remaining cases | 144 |
| Total incisions healed by first intention | 112 or 78% |

Sixteen of these, however, showed a slight amount of serum around one or two clamps.

| | |
|---|---|
| Incisions showing pus around one or two clamps | 17 or 12% |
| Incisions showing pus and serum around one or two clamps | 15 or 10% |
| | 100% |

Total cases showing pus or pus and serum which was sterile..12 or 8.3%

## BACTERIOLOGY.

Total cultures taken, 29.

| | Total | Pus | Pus and Serum |
|---|---|---|---|
| Sterile | 12 | 5 | 7 |
| Unidentified | 2 | 1 | 1 |
| Streptococcus | 1 | 1 | |
| Staphylococcus | 6 | 3 | 3 |
| Streptococcus and Staphylococcus | 1 | | 1 |
| Colon Bacillus | 7 | 2 | 5 |

*702 Rose Bldg.*

Nr. 14

Reprinted from Surgery, Gynecology, and Obstetrics, July, 1911

# USE OF ELECTRIC LIGHTS FOR WARMING THE OPERATING TABLE

By Hunter Robb, M.D.
*Cleveland, Ohio.*

Frequently during the spring, autumn, and winter months the operating room in general, or more especially the operating table, is too cold for the welfare of the patient when a prolonged or even a short operation is to be carried out. Nor is it difficult to imagine that a patient will at times show immediate or subsequent evidence of undue exposure to cold. It is true that she may wear a so-called pneumonia jacket (which, by the way, very frequently is improperly made and gives about as much protection as a good-sized pocket handkerchief), but when placed on a cold table in a room with the temperature frequently in the neighborhood of between 60° and 70° F., the patient always runs a certain amount of risk despite the use of coverings and hot water bags. Those of us whose attention is more immediately taken up with the carrying out of the operation are liable to fail to appreciate to what degree the exposure may be affecting the patient, as we are on the move most of the time, and are thus to a certain extent able to keep up our bodily heat. Then, again, she is still further exposed during the necessary cleansing of the field of operation. Finally, we should take into consideration the loss of heat produced by the inhalation of the ether, it having been shown that this loss to the patient amounts to 21,000 calories of heat for every ounce of ether inhaled.

I have felt for a long time that some practical method should be devised for the prevention of this chilling of the patient, inasmuch as in certain cases this exposure contributes in no small measure to the untoward results that sometimes follow an operation, viz., the development of a bronchitis, a pneumonia, a pleurisy, a nephritis, or a peritonitis, with or without an exaggerated condition of shock. Nor would it be a small matter if we could secure the avoidance of the various minor discomforts, such as a stiffness of the back and neck and the muscular pains throughout the body that are sometimes complained of.

The usual devices that are employed for keeping the patient warm during the operation are rubber bags or flat rubber pads, which are placed under or between the thighs, or along the trunk. In 1886 I remember seeing Dr. Kelly using long, narrow rubber bags filled with hot water for this purpose. The main objection to the employment of such devices lies in the fact that they are difficult to look after properly, and if the bags or pads are too hot, the patient may be burned. Moreover, they may shift their position, and in any case within a short time the water becomes too cool, and the refilling of the bags is difficult and interrupts the operation. Another objection to the use of the flat pad is that the patient does not remain in a fixed position on the table.

In an endeavor to meet most of the requirements that are necessary, we have been experimenting with the use of electric lamps suspended from the under surface of the operating table. After having used this method for more than eighteen months, we feel that it will finally prove to be thoroughly practical and satisfactory.

The lamps are held in an upright position by attachments to two hollow movable metal tubes, which extend from the upper end for a distance of three feet nine inches toward the foot of the operating table (Figs. 1 and 2). Nine lamps of thirty-two candle power are attached to each tube. At the upper end in each tube there is a switch, so arranged that two lamps can be turned on at a time, thus making it possible to control the amount of heat used. The cords containing electric wires are brought through the floor in the middle of the room, and are of sufficient length to allow the operating table to be moved backward or forward in the room. The supports holding the lamps can be removed from the table and the attachment can be so arranged that it can be used wherever there are electric light fixtures.

The patient can be cleaned up or the abdominal cavity irrigated without injury to the lamps. The temperature under the table can be raised 45° F., and on the upper surface of the table protected, with a thick towel, 17.1° F. in twenty minutes, thus rendering the air warm in the immediate vicinity of the patient. The glass plates on the operating table are covered in the middle portion with two coarse towels folded lengthwise, and the upper and lower portions of the table are covered with a piece of muslin folded double; or the pads usually employed may be applied to the table. For about twenty minutes or half an hour before the patient is placed on the table the lamps are turned on. When the patient is placed upon the table the field of operation is cleansed, and dry pads are placed under her. As soon as the operation is begun the lamps are turned out, but on a very cold day, or when the patient is in a very weakened condition, the lamps are kept lighted throughout the operation. If the lamps are turned off at the beginning

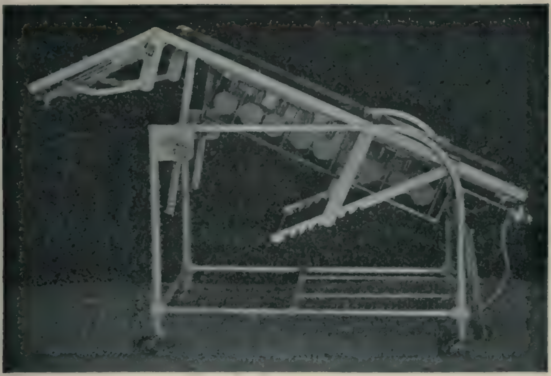

FIG. 1.—Showing lamps, with table in Trendelenburg position.

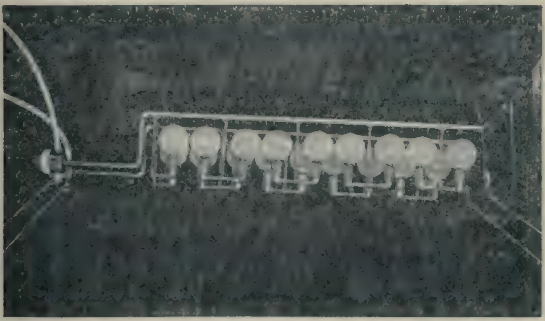

FIG. 2.—Showing lamps detached from operating table.

of the operation they are again turned on for a few minutes while the concluding steps of the operation are being carried out. When this procedure is employed the patient begins to react from the shock of the operation before she is removed from the operating room, and her resistance is probably materially increased in this way. Since we have been using this method of keeping the operating table warm we have not met with a single case of bronchitis following an operation.

## PRELIMINARY ANALYSIS OF THE TEMPERATURE RESULTS OBTAINED AFTER OPERATIONS WITH AND WITHOUT WARMING THE TABLE WITH ELECTRIC LIGHTS

We have made a study of the temperature before and after operation in 138 cases, divided as follows:

| | |
|---|---|
| Plastic operations | 40 |
| Abdominal sections with plastic operations | 62 |
| Abdominal sections alone | 36 |

The most striking results that we have been able to demonstrate in this particular series of cases are as follows:

When the temperature of the operating room is under 83° F., there is always a more marked fall in the patient's temperature. For example, without the use of the lamps, in 38 abdominal sections with plastic operations, there was a total fall of 25.8° F. With the use of the lamps in 38 sections with plastic operations, with the room temperature at 79° F., there was a total fall of 10.6° F., less than half the fall that occurred when the lamps were not used, although the room temperature was 4° F. lower than in the series without the use of the lamps.

Similarly in the abdominal sections alone the fall was twice as much without the use of the lamps, although the room temperature was from three to four degrees higher than when the lamps were employed.

Thus, it would seem, from observations made up to the present time, that there is a distinct lowering of the patient's temperature where the lamps are not employed to keep the table warm.

Nr. 15.

# A Case of Ruptured Ectopic Pregnancy; Streptococcus Infection of the Pelvic Cavity and the Ectopic Sac: Recovery.

By HUNTER ROBB, M. D., Professor of Gynecology, Western Reserve University, Cleveland.

[Reprint from The Cleveland Medical Journal, April, 1911, Vol. X, pg. 316]

The combination of a ruptured ectopic pregnancy with a streptococcus infection, followed by the recovery of the patient, is unusual in my experience at least.

A single woman, aged 24, first came under my observation Feb. 24, 1910, complaining of dull pains in the lower abdomen. She also had a slight elevation of temperature. She gave a history which briefly was as follows:

Six weeks before she was taken sick she slipped on the pavement. Immediately following this accident the menstrual (?) flow appeared, accompanied by a severe pain in the right lower abdomen. The menstrual periods had always been regular with the exception of the one in December, which had been delayed about a week or ten days.

It was learned that the patient had suspected that she might be pregnant and that she had gone to an individual who had applied electricity to the cavity of the uterus in order to produce a miscarriage. Shortly following this procedure she had evidences of an infection as shown by some fever, but after a week's time she seemed apparently well again. Shortly afterwards she had a fainting attack which was followed by a sharp pain in the lower abdomen. She was now obliged to remain in bed on account of the pain in the lower abdomen and the slightly febrile state.

By the bimanual examination I could make out that the uterus was enlarged, and at the right cornu of the uterus I felt a rather firm sensitive mass about the size of the fist. I advised that the patient be sent into the hospital for a vaginal incision or an abdominal section. The attending physician suggested that the condition might be a ruptured ectopic gestation, in which opinion I concurred. I also thought that in all probability there was present an infected tube and ovary.

She was admitted to the Lakeside Hospital three days later, and on March 1, we dilated and curetted and irrigated the uterus and opened and drained the cul-de-sac. About three ounces of blood and necrotic tissue were removed from the enlarged and softened uterine cavity. When the cul-de-sac was opened there was a gush of over a pint of dark fluid blood containing some clots with a few shreds of tissue. The smears and growths which were made from the material from the uterine cavity and the cul-de-sac showed a pure streptococcus infection.

After the operation the temperature fell to about normal and varied from 99° to 101°F. until the seventh day, when it suddenly rose to 103.5°. It fell again to about normal on the ninth day and remained so until the twelfth day when it suddenly went up to 104°F. and the pulse to 140 per minute. We thought that the pelvis was not being drained well enough, so we at once reopened and irrigated the cul-de-sac and re-

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*Read before the Lakeside Hospital Medical Society, Feb. 23, 1911.*

applied a more extensive gauze drainage. The temperature following this procedure rose to 105°F., but the pulse dropped to 120. The same afternoon, however, with a similar temperature the pulse was 160. We then inserted a hypodermic needle into the somewhat indurated area that could be felt in the right lower quadrant of the abdomen and drew off a few drops of blood. This blood showed numerous streptococci. As her condition was undoubtedly becoming worse we decided to open into the mass through an abdominal incision and thus to establish abdominal drainage. This was done under nitrous oxid gas anesthesia. After incising the skin and facia we opened into a sac which contained some bloody fluid and a considerable amount of well organized blood clot. In all, the whole mass was about the size of a closed fist. Swabs taken from the fluid and from the material removed at the time of the operation showed the presence of numerous streptococci.

Immediately after this operation the temperature rose to 106°F. and the pulse varied between 150 and 158 for the next eight hours. The temperature for the next four days was between 103.5° and 105.3°F. and the pulse between 136 and 160. The temperature was generally about 104°F. The temperature then gradually fell, and on several occasions went up to 104.8°F. in the evening. For several days following the abdominal operation the patient showed symptoms which suggested a postoperative insanity. This, however, slowly but entirely disappeared. On the twenty-ninth day following the abdominal operation the patient was sitting up, and the convalescence from then on was uninterrupted.

The points of interest in this case are: (1) Recovery following a ruptured ectopic gestation with a streptococcus infection of the sac and the peritoneal cavity, with a patient so alarmingly ill. (2) The presence of the indurated mass in the right lower quadrant of the abdomen which suggested an inflammatory condition, although in consequence of the finding of the streptococcus in the cul-de-sac and the cavity of the uterus, an abdominal section seemed to be inadvisable at the time of the first operation. (3) The finding of streptococci in the fluid aspirated from the abdominal mass, showing that the peritonitis was spreading and calling for an immediate abdominal operation.

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No. 16.

# The Treatment of Postoperative Septic Peritonitis, With Report of Cases.

By HUNTER ROBB, M. D., Prof. of Gynecology, Western Reserve University, and Visiting Gynecologist to the Lakeside Hospital, Cleveland.

In an experience of some twenty-five years in abdominal operative work I have met with my share of those cases that developed a postoperative septic peritonitis. Such cases, as you know, usually last some four days, or longer, during which time the surgeon tries various remedies and procedures which not only are not always successful in preventing a fatal issue but undoubtedly, at times, add not inconsiderably to the discomfort of the patient, whose condition is already pitiable enough. Finally, when death occurs, although the unfavorable result may be attributed to shock, exhaustion, paralysis of the bowel, pneumonia, inflammation of the kidneys or what not, we cannot but feel that in the majority of these cases at least the primary cause has been a septic peritonitis, and the other factors enumerated were simply consequences.

Nor do I by any means intend to imply that these cases of postoperative septic peritonitis are often the result of any fault of the operator, for when we consider the serious condition in which these patients are at the first operation and when pus is so often found to be present, it is hardly any wonder if a postoperative peritonitis should follow, even when the operative procedures and the technic have been faultless. In my clinic about two-thirds of our abdominal operations have been for chronic suppurative processes affecting the tubes and ovaries.

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*Read before the Section in Obstetrics and Gynecology of the Buffalo Academy of Medicine, March 28, 1911.*

But after all the main question is, How can we save a larger number of these unfortunate patients? You are all familiar with the usual procedures, the hypodermics, the infusions, the local applications, but in my experience these have so often failed me that I have been anxious to find some other, even if it be apparently a more heroic treatment that might promise a larger percentage of successful results.

Experience, or I might say frequent sad experiences, have led me to the conclusion that by appropriate operative measures we can save quite a large number of these infected patients, provided that we decide to intervene early enough, for I cannot but feel that we are inclined to let things go on too long, hoping against hope without any foundation for our expectation of betterment, and only deciding to institute radical procedures when humanly speaking nothing could save the patient.

Of course it will always be somewhat difficult to decide when operative measures should be resorted to, especially as we often find the general condition of the patient to be fairly good apart from the rapid pulse, some vomiting—which, however, may occur only at infrequent intervals—and a more or less marked degree of restlessness. Incidentally I would say: Do not minimize the significance of vomiting especially when lavage is needed to control it.

Often the unfavorable symptoms may be attributed to the shock of the operation, nervousness, or the fact that the bowels have not been sufficiently opened. But it must be remembered that after an ordinary abdominal section we ought to have but little trouble, and I am strongly of the opinion that when these unfavorable conditions develop we should not hesitate to reopen the abdomen, wash out the pelvic cavity and institute thorough drainage. Moreover, in my judgment, it is much better to take chances on an early intervention, for although we shall in this way occasionally do an unnecessary secondary operation, this will usually prove harmless, if not beneficial, and by following this course I feel sure that we shall save a few additional lives.

Although fine distinctions cannot be drawn these patients may be roughly divided into three classes: (1) Those who are in a generally good condition when leaving the operating table; (2) those whose condition immediately afterwards gives us some anxiety; (3) those who are in a critical condition from the time of the first operation. In any case we must first try to exclude the existence of shock as the cause of the condition. This I own is very difficult to do and much depends upon the individual case and the judgment of the operator. Internal hemorrhage, I believe, can often be excluded if careful hemoglobin estimations are made, for we may feel pretty sure that when the hemoglobin is stationary, bleeding has ceased.

In the first class of cases, those in which the patient has been returned to the ward in good condition, if within the first 24 hours the pulse begins to increase in rapidity until it reaches 130 or 140 or more, and if the patient vomits every now and again, after she should have gotten over the effects of the ether; if at the same time the temperature rises and the patient is restless and complains of abdominal pain, in the last few years I have not hesitated to reopen and wash out the abdomen and introduce gauze drains. For an anesthetic, cocain is often sufficient, but when needed, nitrous oxid gas adds practically nothing to the degree of shock.

In other classes of cases, where there is considerable pain after recovery from the effects of the anesthetic, if the condition shows no tendency to improve after the first 24 hours I institute similar procedures. Generally the second operation can be carried out while the patient is in her own bed, and the shock is practically *nil*. The operation is a simple one, and I feel like apologizing for mentioning briefly the details: After everything has been gotten ready, the Kelly pad is put under the patient and the dressings are removed. The edges of the skin incision are slightly separated and from 10 to 20 drops of a 5 or 10% solution of cocain are applied to the tissues. The deeper stitches are then removed, and if the patient complains of much pain, more cocain is applied or injected into the deeper tissues. The peritoneum having been incised a two-way catheter is introduced as far down into the pelvis as possible and the cavity is flushed out with several quarts of sterile salt solution. Finally a strip of gauze is introduced as far down as possible into the cavity and the usual dressings are applied. If cocain proves to be insufficient at any time nitrous oxid gas is administered to surgical anesthesia.

Such an operation usually takes only from 5 to 15 minutes and with the patient in bed well covered and in a warm room, the shock is very slight.

The usual postoperative measures are then employed. I have had quite a few of these patients in whose cases I have not carried out these procedures and the results have been so uniformly unsatisfactory that I feel I am more than justified in risking something, especially as I feel that in the few cases in which I have not accomplished any good I have at least done no harm and have made an honest effort to save an otherwise hopeless case.

I will now very briefly give an account of 15 cases in which this procedure was resorted to. Of these patients 11 recovered and four died.

## RÉSUMÉ OF CASES.

I. Operation, December 12, 1894. Supravaginal hysteromyomectomy (modified Porro operation) for a large myomatous tumor. On the tenth day following the operation patient showed evidences of a beginning peritonitis. The pulse varied between 140 and 150, and she had frequent vomiting, with marked abdominal distension. The abdomen was reopened, irrigated and drained, and the patient recovered.

II. Operation, February 20, 1896. Double salpingo-oophorectomy for a myomatous uterus. Convalescence following the operation was uneventful. The patient insisted upon leaving the hospital at the end of the second week. She had been home only a short time when she began to have cramp-like pains in the lower abdomen, with a rapid pulse and some vomiting; this condition kept up intermittently for about nine weeks, when the abdomen was reopened and drained. The patient recovered.

III. Operation, July 6, 1897. Section for adherent lateral structures. Dense adhesions on the right side. On the second day after the operation the patient began to have severe abdominal pains and vomiting. The pulse varied from 130 to 150, and the temperature from 103 to 104° F. The abdomen was reopened under cocain anesthesia, and more than a pint of turbid-looking fluid escaped. This had an ammoniacal odor, showing that the ureter had been injured. The abdominal cavity was washed out with saline solution and drained. The patient recovered.

IV. Operation, March 28, 1898. Section for chronic adherent tubes and ovaries. The abdomen was drained. The temperature was 101° F., and the pulse 140, 72 hours after the operation. The patient was nauseated and the abdomen considerably distended 48 hours after the operation, and the patient vomited matter which had a fecal odor. The abdomen was reopened March 31. The intestines were very much distended and in one place there was a kink. On slight manipulation the intestine ruptured in one place and gas and fecal matter escaped. Saline infusions were used throughout the operation but the patient died on the table.

V. Operation, June 7, 1902, for adherent tubes and ovaries. Convalescence was uninterrupted until June 11. The temperature ranged from 99 to 100° F., the pulse from 80 to 90. On June 19, as the bowels had not been opened for three days, and as the patient was vomiting a clear fluid, and marked abdominal distension was present a diagnosis of ileus was made, and the abdomen was reopened. The small intestine was found twisted upon itself and adherent to itself, to the pelvic wall and to the pedicle on the right side. During separation of the adherent intestine rupture occurred. The openings were closed and the abdomen was washed out and drained. Death occurred from shock one hour after the second operation.

VI. Operation, March 5, 1904. Section for adherent left tube and ovary, adherent retrodisplaced uterus. The abdomen was closed without drainage. The temperature was 101° F., the pulse 160, 24 hours after the operation, and the patient was complaining of a great deal of abdominal pain. The abdomen was distended, and vomiting had been present since the operation. On March 7, two days after the operation the temperature was 103° F., and the pulse 156. On the same evening the abdomen was reopened and washed out with saline solution. The next day the temperature was 100° F., the pulse 120. Three days later the temperature was 103.8° F., and pulse 132. The abdomen was again flushed out. Some fluid was found in the right pleural sac. Two days later 5 c.c. of fluid were obtained by aspiration from the left pleural sac. The temperature varied between 98° and 102° F., and pulse between 100 and 136 for the next 62 days. On April 16, a small swelling was found extending from the anterior to the posterior axillary line in the sixth interspace. On April 20, this was aspirated but no pus found. On May 3, the swelling was opened, and three ounces of pus escaped. Bacteriological examination of the fluid from the abdomen and the pleural sacs showed streptococci. On May 12, the temperature and pulse were normal. The patient recovered.

VII. Operation, October 14, 1905. Vaginal incision for infection following labor. Several ounces of bloody fluid escaped from the cul-de-sac. On November 21, a section was performed for extensive disease involving both tubes and ovaries. Each ovary was about as large as a good-sized orange. The abdomen was closed without drainage. The temperature was 102°, and the pulse 132, 48 hours after the operation. The patient vomited a small amount of brownish fluid and had several small liquid stools. She complained of a great deal of pain in the right side in the lower abdomen. Pulse 132 to 144. The abdomen was much distended. On November 23, the abdomen was reopened under cocain anesthesia and washed out and drained. The pulse, after the second operation (for a day), was between 150 and 160. The next day the pulse was stronger and slower. The patient recovered.

VIII. Operation, October 17, 1905, for densely adherent tubes and ovaries with adherent intestines and bladder. On the fifth day after the operation the pulse rose to 140, the temperature to 101.5° F. The bowels had been moved freely and good quantities of urine were being passed each day. As the patient was complaining of considerable pain in the abdomen with occasional nausea and vomiting, and as the gravity of the symptoms appeared to be increasing, the lower end of the abdominal incision was reopened, allowing some gas and a dark purulent fluid which a somewhat fecal odor to escape. The cavity was irrigated carefully and drained. A few hours after this the dressings were found to be saturated with a clear ammoniacal-smelling fluid—apparently urine. The next day the pulse and temperature dropped slightly, and urine could be detected on the abdominal dressings. The convalescence progressed smoothly until the sixth day after the reopening of the abdomen when some fecal matter was noticed on the dressings. From then on the urinary discharge gradually decreased, while the fecal discharge varied in quantities for about a month, when it began to decrease. The patient recovered. Seven months after the operation the fistulous tract had entirely closed, and she was gaining strength daily and looked and felt well.

IX. Operation, June 9, 1908, for adherent suppurative tubes and ovaries. Pus oozed from the tubes. The temperature was 102.8° F., and the pulse 140, 48 hours after the operation. On June 11, the abdomen was reopened under cocain and flushed out with saline solution. Profuse hemorrhage occurred from some point in the pelvis, but was controlled by packing with gauze. The infection was due to streptococci. The patient died. Bacteriological examination of the fluid from the abdomen showed large numbers of streptococci and colon bacilli. It is worthy of note that although this case proved fatal the pulse and temperature did not indicate the gravity of the situation.

X. Operation, Feb. 28, 1910, for adhesions and inflammatory processes involving both tubes and ovaries, with suspension of the uterus. The pulse was 148 24 hours after the operation. The abdomen was considerably distended and the patient complained of a great deal of abdominal pain. The abdomen was reopened on the fourth day after the operation under gas anesthesia, and a considerable amount of turbid yellowish fluid escaped. The abdomen was irrigated and drained. The pulse gradually got weaker and two days later she died. In this fatal case also the pulse and temperature were not markedly increased.

XI. Operation, March 1, 1910, for a ruptured ectopic pregnancy. A vaginal incision was made and three ounces of blood and necrotic tissue escaped. Cultures from the uterus and cul-de-sac showed streptococci. Eleven days later the patient had a temperature of 105.7 F. and the pulse rose to 154. The abdomen was opened, allowing some blood clots to escape. The cavity was washed out and drained. The pulse and temperature gradually came down and the patient recovered. Streptococci were also found in the fluid from the abdomen. Such a recovery from a streptococcic infection is somewhat fortunate.

XII. Operation, March 17, 1910, for a left pyosalpinx. The tube ruptured, and some pus escaped into the abdominal cavity. After 24 hours the temperature was 101.5° and the pulse 156. The abdomen was distended and the patient complained of a great deal of pain. Three days after the operation the abdomen was reopened, irrigated and drained. The temperature 48 hours later was 101° and the pulse 120. The pulse and temperature gradually fell to normal. The patient recovered.

XIII. Operation, April 6, 1910. Hysteromyomectomy for an interstitial myoma of the uterus. The temperature rose to 104.1° F. and the pulse to 144, 96 hours after the operation. The abdomen was distended and the patient was vomiting at infrequent intervals and complained of a great deal of abdominal pain. The abdomen was reopened under cocain anesthesia with the patient in her own bed. The pelvic cavity was irrigated and drained. In 48 hours after the second operation the temperature and pulse had fallen to normal. The patient recovered.

XIV. (Secondary abdominal section.) Operation, April 8, 1910, for removal of an adherent retroflexed uterus. The omentum was densely adherent. After 72 hours the temperature was 102° F. and the pulse 88. The temperature varied between this point and 104° F. for a week, and pulse from 126 to 130. On May 3, the abdomen was reopened under cocain anesthesia. The cavity was washed out and drained. After this the pulse and the temperature gradually came back to normal. The patient recovered.

XV. Operation, Oct. 24, 1910, for pelvic inflammatory disease with suspension of the uterus. The temperature was 102.4° F. and the pulse 136 to 140, 96 hours after the operation. The patient complained of a great deal of pain in the abdomen with frequent vomiting and distention of the abdomen. The abdomen was reopened four days after the operation under nitrous oxid gas with the patient in her own bed. A small amount of bloody fluid escaped. The temperature, 24 hours later, had fallen to 101° F. and the pulse to 128. From then on the condition improved without any interruption, and the patient recovered.

## ANALYSIS OF CASES.

No. of cases 15. Oldest patient 43. Youngest 24. Average age 31. No. of pus cases 8. The interval between the first and second operation varied from 1 to 25 days.

| | | | | | |
|---|---|---|---|---|---|
| Highest | temperature | before | second | operation | 105.7° F. |
| Lowest | " | " | " | " | 100.5° F. |
| Highest pulse | | " | " | " | 156. |
| Lowest | " | " | " | " | 130. |

Anesthesia employed: Cocain 6 times, ether 1, ether and chloroform 1, gas 3 times, in 4 others the anesthesia is not recorded.

In 2 cases an obstruction of the bowels was demonstrable. In 3 cases organisms were demonstrable before or at the second operation.

Recoveries 11. Deaths 4. Mortality 36%.

## CONCLUSIONS.

My experience has taught me that critical cases of peritonitis developing after abdominal operations call for early operative interference before the condition becomes hopeless. In patients presenting serious symptoms I do not hesitate to reopen the abdomen and wash out the cavity and institute drainage. This procedure, I believe, has considerably lessened my mortality in such cases.

*702 Rose Bldg.*

No. 17. 1.

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# The Location and Nature of Injuries of the Gastro-Intestinal Tract Following Abdominal Trauma, with the Report of an Injury of the Small Intestine Resembling a Bullet Wound of Entrance.

By C. E. BRIGGS, M. D., Cleveland.

It is the purpose of this brief communication merely to call attention to a few striking points regarding the location and nature of traumatic lesions of the stomach and intestine exclusive of penetrating wounds, together with the report of a case, and not to attempt a broad consideration of the subject.

The relative frequency of these lesions is indicated by a report of 8,000 injuries of all kinds collected a few years ago from the records of St. Thomas's Hospital, London, in which 3.59% were injuries of the abdomen, of which number 23.59% were of the stomach and intestine. Approximately 85% to 90% of the lesions are found in the small intestine, a little more than half the remainder being found in the large intestine, the rest in the stomach. In a somewhat extensive consideration of this subject by Petry in the *Beiträge zur klinischen Chirurgie,* 1896, based on a collection of 219 cases, 172 (78.5%) were of the small intestine, 26 (11.9%) of the large intestine, and 21 (9.6%) occurred in the stomach. Of 113 cases of intestinal injury collected by Curtiss in his Cartwright paper of 1887, 109 (94.4%) were of the small intestine, while only 4 (3.6%) occurred in the large intestine. A small proportion of those in the small intestine are found in the duodenum, about 8%, most of them occurring in the upper meter of the jejunum or lower meter of the ileum. Of those in the large intestine over 50% are found in or near the cecum. Most of the injuries are found in the lower half of the abdomen; those in the upper half, especially in the stomach, are likely to be associated with injuries of the adjacent vicera, spleen, liver, kidneys, or pancreas.

These lesions may be grouped into four general classes, contusions, ruptures, lacerations, and separation of the viscus from its mesentery, although, perhaps, the latter class of cases should be considered solely as injuries of the mesentery. The injuries may involve one or all of the layers progressively in either direction, in or out; the mucosa may be severely injured, the serosa still intact or only slightly hurt, or the serosa and muscular coats may be completely divided, leaving the mucosa intact. When the wall is completely involved the peritoneal cavity is almost always entered, the occasional exceptions occurring in the posterior injuries of fixed portions of the intestine, as duodenum or colon. They are usually single, but may be multiple, rarely exceeding two or three lesions; if multiple, they may be close together or widely separated, even involving different parts of the digestive tract.

Contusions are of all degrees of severity. The graver cases are associated with hemorrhage into or between the layers involved, most frequently separating the mucosa; this may be so extensive as to result in sloughing of the mucous membrane, and as much as 150 cm. has been known to have separated and passed off in this way; or the necrosis may extend gradually through all layers, resulting in delayed perforation. The distinction between lacerations or tears, and ruptures or bursting injuries may be entirely artificial, and is certainly often difficult to recognize, but in a general way such a distinction is thought to exist, although of no practical importance. In ruptures the edges of the lesion are rather clearer cut and more sharply defined, the muscular layers being intact beyond the point of injury. In lacerations the edges are more or less contused, the muscular layers being injured beyond the line of separation; the impression on the intestine of the object causing the injury has even been noted, though this seems rather fanciful.

These lesions in the movable portions of the small intestine occur most frequently opposite the mesenteric border, especially in ruptures, the bursting variety of injury. This portion of the wall has been shown experimentally to be the weakest part of the intestine, and clinical results have apparently demonstrated the correctness of this view. Lacerations, on the other hand, are perhaps more frequently found nearer the mesenteric border, and many of these injuries involve the mesentery. The clean cut ruptures are more likely to lie transversely, involving a varying portion up to complete solution of the entire wall, and tearing of the mesentery. This is probably due to the greater strength of the circular muscular layer, the weaker longitudinal layer giving way more readily. Lacerations are more likely to lie longitudinally or even obliquely, and irregular tears have been observed, even pointed or rectangular flaps of various sizes. Muscular contraction may alter the appearance of the injury, contraction of the circular fibers causing more distortion than the longitudinal layer. In complete transverse injury circular muscular contraction has been noted to such a degree that both open ends have been puckered down as if held by a purse string suture, successfully resisting extravasation. This muscular contraction is less marked in the cases usually classed as lacerations, one explanation being the injury sustained by the muscular layers for a distance from the opening. Tearing of the bowel from the mesentery without injury of the wall is most likely to be found at the junction of fixed with movable intestine, as the duodenojejunal angle and the region of the ileocecal valve. Most of the injuries found in the duodenum have been transverse, complete separation having been observed at both ends. Of those in the continuity of the duodenum, the majority have been on the anterior wall; the writer has observed one case on the posterior wall.

In the large intestine the lesions are usually on the peritoneal surface, but may lie extraperitoneally in the fixed portions. Of the 26 cases in Petry's series, seven occurred in the cecum, eight in the ascending, four in the transverse, two in the descending colon, and five in the sigmoid. In the stomach the injuries are almost always near the lesser curvature, usually near the pylorus, and are said to be about equally divided between the anterior and posterior surfaces. The lesions are usually longitudinal slits lying parallel to the lesser curvature, but there may be great variety in the nature of the opening, and the inner and outer opening may be obliquely separated, connecting an interstitial canal.

Small round openings, such as the one to be described, have apparently been rarely observed. They are said to have been caused by somewhat pointed though not penetrating objects, as the end of a stick; they may be short longitudinal openings which are drawn out laterally by the contraction of the severed circular fibers. They are probably always plugged more or less completely by protruding mucous membrane, as is the case with most intestinal injuries, if not too large.

The case observed was that of a German carpenter, 48 years old, who was struck in the abdomen by the end of a plank about 3:00 p. m. He was immediately taken to an adjoining hospital but he refused treatment and walked home. He was later seen by his own physician and was brought to Lakeside Hospital about 8:00 p. m. The temperature was 101° by rectum, pulse 96, respirations 23. There was a small superficial abrasion in the left upper quadrant of the abdomen, the only visible evidence of injury. The abdominal wall was held rather rigidly and was markedly retracted. Abdominal respiration was very limited, scarcely perceptible in the lower half, and of a board-like character hinging at the symphysis pubis. There was a moderate degree of general sensitiveness, possibly a little more marked in the left upper quadrant. There was dulness on percussion except in the central portion of the upper half. The abdomen was opened at 9:30 p. m., six and one-half hours after the injury. A moderate amount of free bloody fluid was encountered, including some clots. Inspecting the left upper quadrant, a laceration of the small intestine was disclosed, about 3.5 cm. long, extending obliquely from a point about 1 cm. from the mesentery toward the free border of the intestine. The edges were somewhat irregular; the opening was completely plugged by everted mucous membrane, and there was no perceptible escape of fecal matter. The lesion was in the upper part of the small intestine as shown by the arrangement of the vessels, the thickness of the walls, and the presence of the distended lacteals. The opening was closed with linen thread. About 20 cm. from this point the lesion under consideration was discovered. It was about 5 mm. in diameter, situated about one-fourth of the circumference from the mesenteric border, and was completely plugged by protruding mucous membrane. The striking feature was the very close resemblance which the lesion bore to a bullet wound of entrance, and would have been so regarded by any one seeing the specimen out of relation to the surroundings and history. It was closed with a linen suture. Within a distance of about 40 cm. from this injury there were several apparently less important lesions, consisting of abrasions to the peritoneum of the mesentery and the intestine, without visible injury to the blood supply; these injuries were repaired with linen thread. Reasonable inspection failed to show any further injury. The abdomen was closed without drainage. The convalescence was uneventful until toward the end of the fourth day, when a sudden and unexpected change took place, and a condition of extreme collapse supervened. It was suspected that perforation had occurred, possibly at one of the sites of minor injury, the gravity of which was not apparent at the time of operation, but the depression was so sudden and extreme that further interference seemed hopeless, and he died within a few hours. No autopsy was permitted.

*118 Lennox Bldg.*

No. 18

# Retropositions of the Uterus in which Anterior Replacement is Contraindicated.

By CHARLES D. WILLIAMS, M. D., Demonstrator in Gynecology,
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Retrodisplacement of the uterus is a relatively common condition, being found in various stages and in many degrees, from what might be termed a slight retroposition to marked retroversion or retroflexion. Not all of these malpositions by any means necessarily give rise to symptoms, the patients in many instances suffering no discomfort whatsoever. In a large percentage of cases, however, a definite train of disturbances is noted. These may be few in number or manifold, the severity generally increasing the longer the condition remains unremedied.

We all know and have seen the advantageous results which follow the replacement of a retroposed uterus, whether the restoration and retention of position is effected by the simple bimanual replacement and the application of a suitable pessary or by one of the various operative procedures. There remains, however, a certain class of cases, in which forward replacement is contraindicated. That such instances are rare, or perhaps are oftener overlooked than diagnosed, seems to me to be proved by the scanty literature upon the subject. In most of the textbooks the condition is not even mentioned.

These retrodeviations are found only in nulliparae; at least the cases I have observed have all been in young women who have never borne any children. In no instance have I been able to demonstrate the existence of a similar condition in either a primipara or a multipara.

Upon pelvic examination in this class of patients, the uterus has never been found to occupy an extreme retroposition. The position found was that of a mild to a moderate retrodeviation or what may be described as a sagging condition, the organ being generally found about midway in the anteroposterior diameter of the true pelvic cavity and in a direct line with the intra-abdominal pressure and the axis of the vagina.

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*Read before the Clinical and Pathological Section of the Academy of Medicine of Cleveland, May 5, 1911.*

[Reprint from The Cleveland Medical Journal, Vol. X, June, 1911, p. 519]

Upon vagino-abdominal palpation the cervix is very low down in the line of the axis of the vagina, markedly conical in shape, considerably elongated and with its upper or basal part apparently broadened. The supravaginal portion of the uterus seems to ride about the middle of the pelvic cavity and although it moves readily with the cervical portion there is a certain rigidity of movement of the whole uterus due to the surrounding attachments.

Although the uterine body can be readily brought forward by manipulation with the hand placed upon the abdomen assisted by the finger in the vagina, the fundus does not occupy as high a position in the pelvis in regard to the symphysis pubis as in normal cases (hysteroptosis). The body of the uterus is increased in size in both the transverse and the antero-posterior diameter. It gives one the sensation of palpating a non-pedunculated or sessile body resting on the floor of the pelvis. When the fundus is brought forward and the hand upon the abdomen is released the uterus readily goes back into its former position.

The cervix in its elongated condition forms a long lever, so to speak, which greatly facilitates the temporary forward replacement of the uterine body, and which also tends to cause it to remain in its antero-posterior location. The long cervix, inasmuch as it is difficult or impossible for it to remain posteriorly directed across the axis of the vagina, operates to keep the fundus and body in a line with it, or the uterus, as a whole, in the line of the intra-abdominal pressure and in the vaginal axis.

The vagina is somewhat shortened, in some instances very markedly. This shortening predisposes toward a backward displacement of the uterus and in part accounts for the low position of the external os. The uterosacral ligaments upon manipulation give the impression of being thicker, better developed, more tense and resistant than normal. The cervix itself is held nearer the anterior pelvic wall, partly as a result of a poorly developed or short anterior vaginal wall and partly owing to a shortening of the uterovesical ligamentary attachments. When the fundus of the uterus is drawn forward with the abdominal hand, while at the same time the cervix is pushed backward and upward with the vaginal finger, the uterosacral ligaments remain taut and resistant. Upon being released the uterus immediately resumes its former retroposition.

*Etiology*: The explanation of these congenital retrodisplacements must be sought in the embryological development of the uterus. In the embryo in early pregnancy the uterus is generally found anteverted or anteflexed. A maldevelopment undoubtedly gives rise to the malposition.

Kustner has found that an imperfect development of the corpus uteri is generally found in an imperfectly developed fetus and that in a well developed fetus a normal anteposed corpus is the rule.

To embryonal development can be ascribed the normal position of the uterus as well as the congenital class of retrodeviations. The majority of the cases of malpositions are acquired, and I have seen no other class of retrodisplacements which could be said to be congenital in origin.

*Diagnosis*: The symptoms do not give us any definite clue as to the exact pathological condition present in the pelvis, as they are common to many cases of acquired retrodisplacement. We therefore have to resort to bimanual, vagino-abdominal, or recto-abdominal palpation to determine the precise nature of the case.

*Treatment*: First of all, it is highly important that the congenital class be differentiated from the acquired, inasmuch as the treatment, unless based upon a correct diagnosis, may be of no value or may even be detrimental to the health and comfort of the patient.

Operative measures leading to an anterior replacement of a uterus in this congenital position simply add to the number of failures without alleviating the symptoms of the patient, who fails to understand why no benefit—but only an aggravation of her former symptons—has followed from the procedures carried out.

When one understands that an attempt has been made to correct a congenital pathological position of the uterus by the substitution of a pathological position which is more vicious and abnormal than the first, it is not difficult to comprehend the patient's feelings in the matter. It is unfortunate that these cases are seldom correctly diagnosed even at the time of the operation and that only the failure of the uterus to remain forward or an accentuation of the patient's former symptoms leads the operator to finally recognize the exact condition that has existed. Personally I do not consider it difficult to make a diagnosis but my attention was first drawn to these cases several years ago from the failure of a suspension operation.

Altogether, out of a very large series of gynecological cases of all kinds, I have observed this congential retrodisplacement of the uterus in only seven instances. Of the patients three were single and four were married, but not one of them had borne any children or been pregnant. They were all without exception young women and otherwise apparently well developed.

There was no history to establish the preexistence or the presence of any inflammatory reaction, nor were there any evidences of such upon examination or even at the time of operation when this was carried out. In three of these seven cases suspension of the uterus was carried out. In every case not only were the patient's symptoms not alleviated, they were markedly aggravated. In the other four cases the condition was so evident, that, profiting from the ill results in the other three, I did not recommend a replacement.

One of the above cases had been operated upon by a gynecologist in the South who had performed the suspension operation. The patient stated that her symptoms afterward were accentuated. She was told by another gynecologist whose advice she sought that the fundus had been torn away from its point of support which I was also easily able to verify by bimanual palpation.

The uterus in the secod case, in which a suspension had been performed, also pulled away from its point of attachment to the parietal peritoneum a short time after the operation. During the time that the uterus remained forward the patient suffered considerable distress which she expressed as a pulling, dragging sensation at the site of the attachment of the fundus to the abdominal wall. She experienced great relief when the uterus regained its former position, although her earlier symptoms persisted.

In a third the symptoms as related are fairly characteristic of this type of displacement and I shall give them to you along with a brief history.

The patient was aged 23; height 5 feet 5 inches; weight 125 pounds; good development. She complained of a frequent, almost constant desire to urinate with cramp-like pains and a sense of smarting each time she voided. She also complained of dull, aching, bearing down pains in the lower abdomen, especially aggravated at the menstrual periods. She suffered also from backache in the lower lumbar region, generally accentuated when she was on her feet, nervousness, disturbed sleep, variable appetite and attacks of indigestion. Her menses began at 14 years, were regular, lasting seven to eight days, the flow being always excessive in amount, occasionally clots were passed. The dysmenorrhea was always severe.

The Kelly ventral suspension was performed in this case and the patient made apparently an uninterrupted recovery. After leaving the hospital her symptoms continued or were, she said, even worse than before, as in addition to frequent and painful urination she had a sense of pressure over the bladder besides a pulling, drawing sensation referred to the place at which the fundus of the uterus was attached. Her nervousness and other reflex symptoms remained unimproved.

Whether the uterus in this case pulled away from its point of support, and to judge from the other operative cases of the series I expect it did so, or the condition subsided I do not know as the patient left the city about two months after the operation was performed. I might add that there was a depression or slight umbilication of the abdominal wound at its lower third overlying the attached fundus.

The fourth case was one which was referred to me by a physician and which I considered a very typical one. The woman presented symptoms similar to those complained of by the other patients. Upon examination the cervix was found very low in the vagina, elongated, conical in shape; the uterus was slightly enlarged occupying a position midway in the antero-posterior diameter of the pelvic cavity, freely movable but lacking a degree of mobility equal to that possessed by the average normal uterus. The organ gave one the impression of a non-pedunculated or a sessile body resting upon the floor of the pelvis. The uterosacral ligaments were well developed and the lateral structures were absolutely normal so far as their mobility, size and position were concerned. No operative procedure was advised although the patient was anxious to have relief irrespective of the means by which it might be obtained.

A suitable Smith-Hodge pessary was introduced to relieve the hysteroptosis present, which in reality causes the pain. Entire relief by this means was not anticipated at the time of the introduction of the pessary It was tried with the object of holding the uterus upward in the pelvis. Partial relief only was obtained. Later with the patient in a genupectoral position tampons were placed in front of the cervix in the anterior fornix of the vagina. This treatment gave the patient the greatest relief, but of course it would be difficult and tedious to continue the tampon treatment indefinitely in such cases.

I might mention that the urine in these cases showed nothing abnormal chemically or microscopically to account for the bladder symptoms.

Failing, in a routine examination of many thousands of cases, to find this condition of the uterus in women who have borne children I am led to believe that pregnancy leads to a cure. At any rate by a consequent elongation of the body of the uterus with possibly a broadening and subsequent shortening of the cervical portion, the fundus is enabled to come forward more readily and consequently, when suspension or another operation subsequent to childbirth is deemed necessary and is performed. it is possible thereby to maintain the uterus in a normal forward or anterior position without that tension and liability to failure which characterizes the congential class of cases previous to the onset of pregnancy.

I deem it best, therefore, in cases such as these to forego all of the many operative measures devised or resorted to, in that they tend to create what might be termed an abnormal condition, inasmuch as we have to consider the other position as the normal one in this class of cases. The retroposed position of the uterus, placed, as it is, midway in the antero-posterior diameter of the true pelvic cavity is a truly congenital one and leads to fewer symptoms than when the uterus is mechanically more anteriorly placed.

Kelly (Operative Gynecology, Vol. 1, p. 178) in speaking of retrodisplacements in women who have never borne children says: "In these cases the retroposition is often congenital as shown by the short vagina which keeps the cervix so low in the pelvis that the fundus must of necessity fall back: Here the retroposition is natural and an anteposition would be abnormal so that all efforts to induce such a uterus to remain in anteversion will, fortunately for the patient, prove futile." With these conclusions of Dr. Kelly I am quite in accord, except that I do not believe that the low position alone of the cervix determines the position occupied by the fundus. The uterosacral and uterovesical ligaments as well play a part in maintaining the retroposition. With these factors operating to bring the uterus in line with the axis of the vagina, the cervix must occupy a lower position and may even become more and more elongated as we see it in various prolapsed conditions.

In three out of a total of seven cases which I have observed the patients had been operated upon with unsatisfactory results. In two of them the fundus pulled away from its point of attachment, with partial relief to the patients. In the third case the uterus, up to the time when the patient left the city, remained forward but the previous symptoms were aggravated and new ones added. In the remaining four cases replacement of the uterus was plainly contraindicated and was advised against.

In any case of this class of retrodisplacement it should be impressed upon the patient, or her friends or relatives, that relief or cure cannot be expected from any operative procedure carried out except from a complete hysterectomy which, of course, would be out of the question.

The cure for the condition, therefore, seems to lie in the development of a future pregnancy, inasmuch as the cases are not met with in parous women.

It is true that the elongated, low down, axially-placed cervix predisposes to sterility, but this is only a relative and not an absolute condition.

In our endeavor to relieve and cure patients suffering from retrodisplacements we must carefully eliminate these cases of congenital origin. I would say that because a patient exhibits no symptoms when the uterus is in retroposition it is not necessarily to be inferred that the displacement is a congenital one. The differential diagnosis though too seldom made, is nevertheless not difficult, the bimanual vagino-abdominal method of palpation, with or without anesthesia, being employed.

A failure to correctly diagnose these cases means not only an unnecessary operation which is to be deprecated at all times, but also entails additional suffering upon our patient who has sought relief. It is only through close observation and much experience that these cases can be eliminated and kept from the infliction of an operation which can offer neither relief nor cure.

### SUMMARY.

1. Cases of acquired retrodisplacement often present no symptoms, but in the congenital type symptoms of the abnormality are always complained of and are due to hysteroptosis which exists. The position of the uterus when it is constantly acted upon by the intra-abdominal pressure, tending

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to force it more and more downward, must cause discomfort to the patient.

2. Congenital retrodisplacement is somewhat rare and is seldom diagnosed. Cases of retrodeviation, even though present from childhood, are not necessarily to be classed as congenital.

3. The condition is never found in primiparae or multiparae, only in nulliparae. Pregnancy effects a natural cure.

4. The sterility present in these cases is only a relative, not an absolute condition.

5. Operative precedures are to be condemned and should have no place in the treatment of this type of retroposition. A diagnosis is not difficult and should preclude operation. The patient's sufferings are much accentuated after operative replacement.

6. Tampons and pessaries give some temporary relief by partially correcting the hysteroptosis.

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[illegible]

## PART 2

# PATHOLOGICAL AND EXPERIMENTAL PAPERS

No. 21.

# Drug Exanthemata in Relation to Anaphylaxis.

By HAROLD N. COLE, Ph. B., M. D., Hanna Research Fellow in Pathology, Cleveland.

From the Pathological Laboratory of Western Reserve University.

## I. REVIEW OF ANAPHYLAXIS.

In 1904, while Ehrlich was visiting America, Theobald Smith called his attention to the fact that many of his guinea pigs sickened and at times died suddenly after receiving doses of diphtheria antitoxin. The result, on Ehrlich's return to Europe, was Otto's work on "The Theobald Smith Phenomenon," an article by Rosenau and Anderson[18] appearing independently and almost simultaneously.

Even before 1905 certain facts had been noted concerning this phenomenon and the name "anaphylaxis" had been given to it by Richet in 1904 while working with a protein derived from the tentacles of the sea anenome *Actinia*. Its significance, however, had not been grasped and it has remained for American students to collect a large part of the data that have accumulated in the last five years concerning this interesting and important problem. Otto[19] was the first to show that the phenomenon was not dependent on the antitoxin but on the serum used, for the same results were achieved by the use of normal horse serum as by the use of antitoxic serum.

As defined, anaphylaxis is a state of hypersusceptibility of the organism to foreign substances and is brought about by the introduction of foreign proteins and their cleavage products. These substances must be protein in nature though not quite all of them will cause the condition, e. g. leucin and tyrosin.

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*Read before the Experimental Medicine Section of the Academy of Medicine of Cleveland, March 10, 1911.*

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For example, let us give a normal guinea pig a sensitizing dose of 0.5 c. c. of horse serum either subcutaneously, intraperitoneally, intravenously or by the intracranial route. After an incubation period of from seven to nine days let us reinject the sensitized animal with from 0.01 to 0.1 c. c. of the same serum. The pig becomes restless at once, scratches at his mouth, trembles, and appears to be in distress. His breathing becomes irregular, rapid, and shallow. The sphincters refuse to act. The pig has convulsions, with cessation of breathing, and dies quickly in so-called anaphylactic shock, the heart continuing to beat for some time after respirations have ceased.

If the first or sensitizing dose, or the second or toxic dose of the serum has been too small, perhaps the pig, though showing severe symptoms, will recover. Then he passes into a stage of immunity, for the time being, in which he will no longer react to a dose of the same serum. But in this connection Wells[30] working with egg-white, was able to sensitize a guinea pig with from 0.00000005 to 0.000001 gram so that 0.5 mg. was a minimum lethal dose for the second or toxic dose. If, on the other hand, the sensitizing dose is too large, e. g. 25 c. c., Alphen[3], working with cattle, and Otto, Gay and Southard, working with guinea pigs, have shown that the incubation period is much lengthened or even that the animal passes into a state of immuinty as regards any further action from the toxic injection.

The incubation period for anaphylaxis varies in different species from seven days to two or three weeks and is shorter after intravenous than after subcutaneous injection. Once the animal is sensitized he remains hypersusceptible to an injection of the same serum for an indefinite period; at any rate 732 days in the guinea pig. Alphen mentions the case of a cow dying in acute anaphylactic shock from 10 c. c. of "milzbrand" serum, the sensitizing dose having been given 13 months before.

On examination of the stricken animal it is found that there is a lessened coagulability of the blood[5]. Pearce and Eisenbrey[24], Biedl and Kraus[6] and others have found a lowered blood pressure. Especially in rabbits, and also at times in other animals, at the point of the injection of the serum there is a markedly edematous reaction area. This reaction in rabbits may go on even to the formation of a sterile abscess (phenomene d'Arthus[4,5]). In cattle, horses and man there may be numerous areas of edema about the eyes, nose, and mucous membranes of the mouth, throat and vulva. The blood picture is that of a leukopenia, followed later by a leukocytosis. The blood platelets are increased.

Through pathological examination, Auer and Lewis[8] have shown that the acute anaphylactic death is due to asphyxia caused by the development of a stenosis in the pulmonary air passages, so that practically no air enters or leaves the lungs and they remain distended. This action is peripheral for it occurs after destruction of cord and medulla, and it is probably caused by tetanic contractions of the smooth muscles of the bronchioles. Schultz[22] has strengthened this theory by showing that segments of smooth muscle of the intestine from the sensitized guinea pig contract more vigorously upon treating them with dilute horse serum than do segments of muscle of non-sensitized guinea pigs. In addition, guinea pigs dying in anaphylaxis, show hemorrhages into their lungs and stomach walls with fatty changes in the heart muscle. In cattle and goats, Alphen has invariably found edema of the lungs.

Mention has been previously made of the fact that a guinea pig which survives its second dose of serum, after having shown symptoms of anaphylaxis, passes into a stage of immunity associated with anaphylaxis "allergie." For example, in for months or even years. This condition may be attained in another manner. If we reinject the animal at intervals of two or three days, instead of waiting for its incubation period to elapse, we find that it is no longer susceptible to the toxic dose of serum and that it is now immune. The guinea pig is then said to be in a state of anti-anaphylaxis or immunity. The condition has been studied very thoroughly by von Pirquet[17], especially in reference to vaccinia, tuberculin reactions, and serum disease in man. He has named the condition of acquired immunity associated with anaphylaxis "allergie." For example, in a man vaccinated for the first time, a reaction, starting in about four days with the formation of a macule, passes successively through the stages of vesicle, papule, and pustule, the condition reaching its height in about 10 days with general symptoms of fever, malaise, enlarged glands, leukopenia, etc. However, if the man has been previously vaccinated and his immunity is good, then in this state of "allergie" or acquired immunity there is a time change in the resulting reaction. The process appears and ends in 24 hours. There is a qualitative change in that only a small evanescent papilla with no areola forms, and a quantitative change in that the reaction is only local. The practitioner should take advantage of this: by watching his patient during the first 24 hours, if the entire reaction is gone through with in miniature then the patient's immunity is good and another vaccination is not required.

To return to our guinea pigs, if we take a sensitized pig and, after the close of the incubation period, withdraw some of its blood and inject it into another guinea pig, it is found that after 24 hours the latter animal is susceptible to an injection of the serum that sensitized the first animal. In other words, there has been a transference of some material, floating free in the blood, from the first to the second pig. The condition is called passive anaphylaxis and it is found that even a guinea pig with an acquired immunity to a serum can passively sensitize another pig to that serum. It is thus seen that anaphylaxis and immunity are two closely correlated phenomena, the latter being only a further stage of the former.

It has been said that a period of at least 24 hours must elapse between the injection of sensitized serum of another animal and the toxic dose of the sensitizing serum, in order to cause passive anaphylaxis. However, Anderson and Frost[1] repeating work done by Biedl and Kraus[3], and Doerr and Russ, have shown that immediate shock can be produced by the injection of a mixture of sensitized serum and of the serum that caused the sensitization. Moreover Anderson[2] has shown that the young of sensitized female guinea pigs show a passive anaphylaxis. This has been confirmed by other workers including Schenk[21], who also avers that there is a passive transference through the sperm of sensitized males. Others dispute this latter assertion.

Anaphylaxis is a specific reaction. By this we mean that if a guinea pig is injected with horse serum then he will react to a dose of horse serum only. In fact Rosenau and Anderson[20] have been able to inject three different proteins into a pig and then to get successive reactions for each one on injection of the second dose. Thus far it has been caused by the use of many different proteins including horse serum, egg white, split proteins (especially by Vaughn[28]), milk, donkey serum, sheep serum, rabbit serum and guinea pig serum, eel serum has been used especially by Doerr and Raubitschek[11], and Richet[17] has worked with proteins derived from the tentacles of *Actinia*. Metchnikoff[13] has prepared an immune serum against spermatozoa. The toxic principles of the proteins are not affected by various chemicals, ferments, freezing and drying; indeed Uhlenhuth and Handel[9], as proof of the extraordinary resistance of the sensitizing body, used extracts of dried mummy, of 80 year old cow's placenta, and of dried, 14 year old blood the cells of which had been completely destroyed. Neither chloroform, trikresol, nor formaldehyd hinders the anaphylactic action of horse serum. It appears to be impossible to cause anaphylactic symptoms by the use of leucin and tyrosin. Rosenau and Anderson feeding guinea pigs uncooked meat were able to cause anaphylaxis by the injection of albuminous extracts of the same meat.

Anaphylaxis is not due to any cumulative action, since Richet[17], working with mytilo- and actino-congestion, has pointed out that he was able to get a marked or fatal result after two injections, provided there was a definite incubation period between them, whereas both doses injected at the same time had no effect. Nor is it any toxin action, at least the anaphylactic antibody is not connected to the toxin body, for Doerr and Raubitscheck[11], working with poisonous eel serum, found that, although it lost its toxic properties when heated to 58° C., it was still able to cause anaphylaxis.

The theories as to the causation of anaphylaxis are many, e. g., that it is analogous to the precipitin reaction, that it is due to ferment action, etc. In this paper, which is intended only as a very short summary, space will not permit of the explanation or discussion of these theories. Permit me in this place, however, to quote Anderson and Frost[1]: "Hypersusceptibility to a normal proteid consists in an increase of the power of assimilation of that proteid, especially an increase in the rapidity of the reaction. This is due to the formation of a specific antibody, demonstrable in the somatic tissues (smooth muscle) and in the serum of sensitive pigs. The action of this antibody on its antigen is quantitative and is probably primarily proteolytic. Anaphylactic shock is due to a disturbance of the metabolic activities of vital cells rather than to the specific (permanent) intoxication. Anti-anaphylaxis is a state of insusceptibility due to saturation of the specific combining receptors. The passive transfer of anaphylaxis as also its hereditary transmission is a transfer of the anaphylactic antibody. Anaphylaxis is a step towards immunity which is conceived as an increased capacity for safely and rapidly eliminating the specific antigen proteid."

Many think that the urticarias which occur in susceptible people, after the eating of certain foodstuffs such as lobster, etc., are an anaphylactic phenomenon. Thus Smith[25] tells of a man, aged 47, who first at nine years of age had a severe urticaria, vomiting and general depression after the eating of buckwheat cakes. Since then he has always been very susceptible to and, by means of his reaction, was even able to detect the adulteration of pepper with buckwheat. The patient was vaccinated with buckwheat flour, using wheat flour for control. Within 15 minutes he had a very severe general depression, areas of edema, etc., while locally at the site of vaccination there was a large wheal.

Wechselmann[29] and Siegheim[24] in this connection mention a peculiar dermatitis found among susceptible carpenters working with a foreign wood called "satinholz." Once the men become susceptible they are no longer able to work around the wood without a resulting severe dermatitis and general reaction.

Sellei[23] has also found that persons affected with psoriasis reacted to injections of psoriasis efflorescences with local redness and edema, while in one case there was a temperature of moderate height. All cases showed some general reaction and several had new eruptions of the disease.

## II. INVESTIGATIONS OF OTHER WORKERS ON THE RELATION OF DRUG EXANTHEMATA TO ANAPHYLAXIS.

We all know that some people are susceptible to the exhibition of certain drugs and reasoning from the last mentioned phenomenon Bruck[9] has conceived the idea that possibly the hypersusceptibility of such persons, resulting in drug exanthemata, is an anaphylactic reaction. Beginning first with tuberculin exanthems he says that Bauer[7] by injecting serum from tuberculous men into guinea pigs, was later able to get severe symptoms and characteristic elevations of temperature by injecting tuberculin into these pigs. Some workers agreed and others disagreed with this and Bruck was unsuccessful in his experiments until he had a patient with lupus and lichen scrophulosum. The patient had never been injected with tuberculin and a few hours after receiving 0.5 mg. of Koch's tuberculin O. T. he reacted with general fever, headache, malaise and a disseminated morbilliform eruption. The latter faded in 24 hours and appeared in eight days on giving a like injection. There was also another similar case which reacted after the same dose with an explosive scarlatiniform eruption. Five c. c. of serum from these patients was injected into guinea pigs and 24 hours later the animals received 0.5 c. c. Koch's tuberculin O. T. They sickened in the first hour with characteristic symptoms and died in four or five hours, while the controls remained well. Autopsy findings were negative.

Bruck then goes a step further and reports the case of a man with a marked explosive iodoform rash. Some of his blood was removed and 5 c. c. of serum injected into each of three guinea pigs. After finding the lethal dose of iodoform to be 0.3 gm. per kilo, he, 24 hours later, injected them with about 0.33 gm. per kilo. The first and third pigs in five minutes showed typical anaphylactic symptoms while the second pig showed only slight uneasiness. The controls remained well for the time, though all the pigs later died from iodoform poisoning. Autopsy findings were negative. Bruck concludes that the iodoform intoxication is not brought about by the iodoform itself but that, in its absorption, albumins in the body become iodized so that they lose their specificity for proteins and react to a further dose of iodoform with anaphylactic symptoms. "Iodoform anaphylaxis then is nothing more than a subspecies of the recognized albumin anaphylaxis."

Shortly after this work Klausner[11] had an opportunity to test another man with an iodoform eruption. The guinea pig injected with his serum, and 24 hours later with iodoform, sickened and was dyspneic in the course of two hours, showed paretic symptoms in six hours and died in twelve hours. The controls remained normal.

In his experience with several cases of lupus he reached the following conclusions: That in cases of lupus reacting normally to tuberculin injections, i. e., where there was no oversusceptibility, passive transference was impossible. But in three cases reacting with a general skin eruption the oversusceptibility was passively carried over to the pigs.

Later Klausner[14] had some cases showing hypersusceptibility to potassium iodid. His first patient had, in 1908, two different iodoform intoxications. Later with 1.0 gm. of potassium iodid he had a bullous iodin erythema. Five c. c. of his serum was injected into a guinea pig, while a second pig received normal serum from another patient, a third pig acting as a control. In 48 hours all the pigs received 0.5 gm. of potassium iodid in 50% solution. The author had previously found that 0.5 gm. caused death of guinea pigs in one hour from the action of the potassium on the heart, but that for one hour they remained normal. Following the injection the first animal died almost at once while the others, though very restless at first, later quieted down and did not die for several hours. In a second and in a third series of like experiments he had about the same results, in each case autopsy findings being negative. After several more experiments he came to the following conclusions: "In the six experiments there was a similarity of the symptom-complex throughout; in the main the sensitized animals immediately after the injection remained motionless and died at once or they sat motionless for some time and died in the course of an hour, while none of the eight control animals showed such symptoms in the course of an hour." Klausner thought that there was a hypersusceptibility of the affected organism to be found in these cases and that possibly some poison was passively carried over to the guinea pigs. Whether, however, an anaphylaxis was involved only further experiments could tell.

An even more striking case has been lately described by Bruck[10], that of a patient who had such a marked susceptibility to antipyrin* that he had used none since 1894. However, on

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*Since this page was written Klausner (*Münch. med. Wochenschr., Jan. 1911, III, 138,*) has reported the case of a man 29 years old with marked antipyrin idiosycrasy since the age of 10 years. Some of his blood was removed and injected into each of three guinea pigs. Having found that 0.3 gm. of antipyrin could be safely taken by pigs, with only a little stupor at times, he injected 24 hours later such an amount into one of the pigs and into two controls. The pig had true injecting 5.0 c. c. of his serum into a pig and then in 24 hours giving the pig an injection of antipyrin, the animal became very uneasy in 45 minutes, dyspneic in one hour, finally had tonic and clonic convulsions with paresis of the hind legs and died in five hours. The controls remained well. This experiment is very suggestive, showing not only a very marked hypersusceptibility which was passively transferable to the pig, but also a hypersusceptibility which was still present after a lapse of 16 years. Thus far the longest known case of hypersusceptibility in man to serum disease, as recorded by von Pirquet and Schick[*], is about seven and one-half years. Bruck in this same paper says that he had been unable to passively transfer this susceptibility in several cases of hydrargyrum idiosyncrasy and Leibkind in Neusser's clinic also had no results in one case.

Both Bruck and Klausner say that the best results are achieved in cases showing an explosive reaction; and both men agree that only further investigation can confirm the reaction.

## III. PERSONAL INVESTIGATIONS ON THE RELATION OF DRUG EXANTHEMATA TO ANAPHYLAXIS.

During the past few weeks we have had the opportunity of testing several cases of drug exanthemata at the Lakeside Hospital Dispensary and would like to present the following:

The first patient, A, a man aged 47 years and of good constitution, complained of pain in the hand and of a pustular eruption on face, arms and hands of four days duration. Family history is negative. Two years ago he had acute articular rheumatism and was in the hospital for several weeks. He drinks a little but uses no tobacco; his appetite is good and bowels are regular: he has no cough, expectoration or night sweats; he has no urinary symptoms, but has had gonorrhea. The present illness dates from two weeks ago when a horse fell on his right hand, bruising it severely. Since then he has been having it dressed

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clonic and tonic convulsions and died in several hours. Controls remained well. The next day he injected another of the sensitized pigs and two more controls. This pig likewise died in several hours, while the controls showed nothing. In eight days the third pig and two more controls were injected with antipyrin. Here the sensitized pig merely had tonic and clonic convulsions and recovered, controls again showing nothing. He was also able to carry the hypersusceptibility from a pig, sensitized with the patient's serum, to another pig so that on injecting the second pig with 0.3 gm. of antipyrin he died. In a case of veronal exanthem and also in a case of hydrargyrum susceptibility he was unable to passively transfer it to guinea pigs. He concluded that it was because the exanthems were not explosive enough in character.

at the surgical dispensary. For about 10 days he has been feeling rather weak and apathetic with more or less headache. Four days previous to the taking of this history the patient was given a prescription containing potassium iodid in such proportions that he was getting 6.0 gms. a day. Within a day the patient noticed a reddening of the skin, coryza, and conjunctivitis and in four days he presented himself again at the dispensary because of a pustular eruption on the face, arms and hands, together with nausea, and pain in the back. The history and picture presented was much like that of a variola and Dr. Henry A. Becker, on whose service the patient was, asked Dr. W. T. Corlett to see him. A diagnosis of potassium iodid rash was made and the patient was

TABLE I.

| Pig No. Weight | First Injection | Interval | Second Injection | Symptoms |
|---|---|---|---|---|
| 1<br>325 gms. | 5 c. c. serum A | 24 hours | 5 c. c. of KI 50% sol. | Was rather restless after the injection, later quieted down and showed some paralytic symptoms after 2 hours. In 4 hours very apathetic, unable to stand and died in 12 hours. |
| 2<br>300 gms. | 5 c. c. serum A | 24 hours | 4. c. c. of same | Very restless after injection, jumping up and down. Scratched at face in 20 minutes. Later very apathetic, partly paralytic, respirations irregular and died in 95 minutes. |
| 3<br>300 gms. | 5 c. c. serum of normal patient | same | same | Outside of abnormal quietness following injection, appeared normal. Gradually weakened and died in 3 days. |
| 4<br>375 gms. | none | none | 5 c. c. of same | Restless in one hour, then laid down on side. Apathetic and died in 6 hours; there being some symptoms of paralysis. |
| 5<br>375 gms. | none | none | same | Very restless and attempted to bite spot of injection. Cried out. In 2 hours listless and hind legs were unstable. By next day he was stable once more and lived for two days. |
| 6<br>420 gms. | 5 c. c. serum A | two weeks | 8 c. c. of 5% sol. KI | Appeared about normal for nearly a day, then began to weaken, was unable to stand and died in 24½ hours. |

sent home for two days with no medicine and told to come back for admittance to the hospital at the expiration of that time. Examination notes made then are as follows: On the extensor surface of the right arm, ulnar edge of left arm, forehead and left side of face there are numerous shotty pustules varying in size from 0.5 to 1.0 cm. in diameter and in all stages of formation. The entire skin of the body shows a moderate erythema and blotching, while the vasomotor tone is poor. On both palms there are several areas resembling commencing pustules. Temperature is 100.8° F. and pulse 96. Glands are generally enlarged. Otherwise examination negative. A biopsy was made of two of the pustules and the patient sent home. He returned to the hospital in three days and was admitted on the service of Dr. W. T. Corlett. At the time only a few dried up pustules remained to show the former condition. On once more exhibiting the potassium iodid, the patient reacted as before with a coryza, conjuctivitis, headache, and general erythema, which became pustular. On December 4, 1910, 100 c. c. of blood was removed from his arm and after standing for 24 hours 5 c. c. of the serum was injected subcutaneously into guinea pigs No. 1, 2, and 6. Blood was also taken from a normal man and 5 c. c. of his serum injected into pig No. 3. Pigs Nos. 4 and 5 served as controls. Pigs Nos. 1 to 5 in 24 hours received 5 c. c. of a 50% solution of potassium iodid subcutaneously while No. 6 was not injected for two weeks.

The dose of iodid used was very large and invariably caused an intense edema at the site of injection from hypertonicity of solution. So in all succeeding experiments a 5% solution of the iodids was employed. It will be seen from the table that pig No. 2, and possibly No. 1, had symptoms that could be construed as akin to anaphylaxis, though one of the control animals, No. 4, died before No. 1. Pig No. 6 showed nothing after an incubation period of two weeks between the first and second dose, but this is as one would expect if there is anything in the reaction; for in two weeks the passive sensitization would have worn off. However, the dose of potassium iodid used having been so large that the results were not felt to be conclusive, two weeks later another 100 c. c. of blood was removed from the Patient A, his iodid having been stopped in the meantime.

Another patient with an iodid rash came under my observation about the same time and I give his history and chart the results found in the same table with those of Patient A.

Patient B, a man aged 33, was kindly turned over to me for investigation by Dr. John Phillips from the Lakeside Hospital Medical Dispensary. The complaint is swollen testicle and eruption on the legs. His family history is negative. Thirteen years ago he had acute articular rheumatism and seven years ago he had a chancre on his penis, with gonorrhea at the same time. Several weeks later he had an eruption on the body with sore throat. Patient frequently has sore throat, he coughs somewhat, and has night sweats. There has been loss of weight, his appetite is good and bowels are regular. He has no urinary symptoms. He is troubled with shortness of breath and palpitation of heart.

Present illness:—About two months ago he began to notice a swollen rather painful testicle and came to the dispensary. Patient was found in a bad condition from mitral disease and was referred to the hospital. Later, on returning to the dispensary, his Wassermann reaction, done by Drs. R. Dexter and C. L. Cummer was strongly positive. Potassium iodid, grains ten three times a day, was ordered for his swollen testicle. However, after he had taken three doses he noticed a petechial eruption on the inside of the legs and thighs. Otherwise he felt well. A sample of 100 c. c. of his blood was also removed. His idiosyncrasy to potassium iodid was later confirmed by its exhibition a second time.

Six guinea pigs were injected, each with 5 c. c. of serum from patient A, but as two of them died before the injection of iodid, only four were used. Three pigs were injected, each with 5 c. c. of serum from patient B and one was treated with 5 c. c. of serum from a man affected with aortic disease who had been taking potassium iodid 2.0 gms. thrice daily for six months and who was not susceptible. In 24 hours all the pigs were injected subcutaneously with 1.0 gm. to the kilo. of either potassium iodid (KI) or of sodium iodid (NaI), as a 5% solution. The sodium salt was used on Dr. T. Sollmann's suggestion to see if the action, if any, were due to the iodin ion or to the metallic ion.

TABLE. II.

| Pig No. Weight | First Injection | Interval | Second Injection | Symptoms |
|---|---|---|---|---|
| 7<br>350 gms. | 5 c. c. serum A | 24 hours | 7 c. c. of 5% sol. KI, | Pig very restless after injection, scratched at cage, jumped up and down. In 15 minutes no further symptoms and alive 5 days later. |
| 8<br>410 gms. | same | same | 9 c. c. of 5% sol. NaI | Outside of slight restlessness he showed no symptoms and was alive 5 days later. |
| 9<br>230 gms. | 4. c. c. serum A | same | 4.5 c. c. of 5% sol. KI | Was quiet for 15 minutes, then fell over on side panting. Tonic convulsions in 18 minutes. Later recovered somewhat but was very apathetic and died between 11 p. m. and 8 a. m. Was injected at 11:30 a. m. |
| 10<br>320 gms. | 5 c. c. serum A | same | 6 c. c. of same | Ate a little after injection, later listless and in 2 hours fell over on side. No other symptoms and was alive 5 days later. |

| | | | | |
|---|---|---|---|---|
| 11<br>460 gms. | 5 c. c. serum B | same | 9 c. c. of same | At no time did he show any symptoms. |
| 12<br>230 gms. | 4. c. c. serum B | same | 4.5 c. c. of 5% sol. NaI | Showed no symptoms for 7 hours when he fell out of cage. Later he was rather listless and died in 26 hours. |
| 13<br>235 gms. | 4. c. c. serum B | same | 4.5 c. c. of 5% sol. KI | In 25 minutes restless, one hour unstable falling over and struggling. In 80 minutes bucked up and down and from then on dyspneic, lying on side and struggling at times. Death in 9 hours, 35 minutes. |
| 14 | 4. c. c. serum A | | | Died within 24 hours; cause unexplainable; autopsy negative. |
| 15 | same | | | Died within 24 hours; cause unexplainable; autopsy negative. |
| 16<br>370 gms. | 5 c. c. serum patient taking KI, 2.0 gms. t. i. d. for 6 months | same | 6.5 c. c. 5% sol. KI | At no time were there any symptoms. |
| 17<br>230 gms. | none | none | 4.5 c. c. of same | No symptoms. |
| 18<br>220 gms. | none | none | 4. c. c. of same | Rather listless after injection, otherwise showed nothing. Alive 5 days later. |
| 19<br>220 gms | none | none | 4. c. c. 5% NaI | Normal for 2 days then weakened and died in 3 days. |
| 20<br>190 gms. | none | none | 3.5 c. c. of same | No symptoms. |
| 21<br>360 gms. | none | none KI | 7 c. c. 5% | Slightly listless following injection but alive 2 days later. |

From the preceding table it will be seen that pig No. 9 injected with serum from A and pig No. 13 with serum from

B showed very acute symptoms while pig No. 7 receiving serum from A had slight symptoms though they might be ascribed to the irritant action of the potassium iodid. None of the normals showed any symptoms and the pig injected with serum from the man with aortic disease had no symptoms. It is rather significant that the pigs injected with sodium iodid appeared to be little affected and more work should be done in this connection to see which ion is concerned in the reaction, if it may be called a reaction. Unless otherwise stated the pigs were alive at end of five days.

The opportunity presented itself of still further carrying out our research in the person of patient D, a man aged 20. This man presented himself at the Lakeside Hospital skin clinic complaining of a general skin rash of one day's duration. Patient has had measles, otherwise always well. Uses no tobacco or alcohol. Appetite is good, bowels regular, no cough or expectoration. About two weeks ago he had a gonorrheal infection and for one week he had been taking a patent medicine internally. The night before coming to the clinic he had a severe itching of the skin with a general eruption. No coryza, sore throat or malaise. On examination patient was well nourished and developed. The entire body was covered with a discrete and in places confluent morbilliform eruption, together with an erythema of the whole skin. No conjunctivitis, Koplik spots, or sore throat. There was no rise in temperature. General glandular enlargement was found. Lungs and

TABLE III.

| Pig No. Weight | First Injection | Interval | Second Injection | Symptoms |
|---|---|---|---|---|
| 22<br>470 gms. | 5 c. c. serum patient D | 24 hours | 1 c. c. of 10% copaiba | Never any symptoms and alive 2 days later. Urine showed only a few triple phosphates. |
| 23<br>445 gms. | same | same | 0.5 c. c. of same | No symptoms. |
| 24<br>305 gms. | 5 c. c. serum normal patient | same | same | No symptoms. |
| 25<br>340 gms. | none | none | same | Very restless following injection. Otherwise normal. |
| 26<br>505 gms. | none | none | 1.0 c. c. of same | Rather quiet after injection. Otherwise normal. Urine negative. |

heart were normal. A diagnosis of copaiba rash made by Dr. W. T. Corlett. The patient was given an ointment to be used externally, the medicine was stopped and he was told to return in two days. On his return the eruption was nearly gone and there was a slight desquamation of the skin. To clinch the diagnosis the patient was given capsules containing copaiba, grains ten, one to be taken thrice daily for two days. He appeared at the clinic two days later with an intense reaction and 100 c. c. of his blood was removed. Five c. c. of the serum from this was injected into each of two guinea pigs while a third pig received serum from a normal man and two other pigs served as controls. A 10% solution of copaiba in olive oil was used for the second or toxic dose.

None of the pigs showed any symptoms and they were all alive two days later. Urine examinations revealed no nephritis and possibly this is an indication that no copaiba was absorbed, since it is very irritant to the kidneys.

## CONCLUSIONS.

In all pigs dying, a careful macroscopic and microscopic examination revealed nothing internally but a general congestion. In the guinea pigs in which potassium iodid or sodium iodid was used there was always an intense local edema at the site of injection, due to the use of the hypertonic solutions. Pigs showed no hemorrhages or edema of the lungs. Stomach walls revealed no hemorrhages and there was no fatty change in the heart muscle.

From careful study of my three tables of experiments it must be admitted that four or possibly five of the pigs died in a sudden, acute manner that is quite unexplainable, for example No. 9 in Table II, while none of the controls showed such symptoms. To say that such symptoms are due to anaphylaxis, however, raises a question whose solution requires still further investigation by means of carefully controlled experiments. I will entirely agree with Bruck and Klausner in their contention that tuberculin exanthems are due to anaphylaxis and that the hypersusceptibility can be passively transferred. Here we are dealing with a protein and von Pirquet[27] has studied the condition very carefully in his work on allergie. If there be a tuberculous focus present in the organism then the continuous slight stimulation from the tubercle bacilli tends to cause the formation of antibodies in the patient, with the result that, on injection of tuberculin, there is a receptor already present for the protein, resulting in a higher or lower degree of anaphylactic reaction. As has been worked out by von Pirquet, under the following conditions only do we get no symptoms on such injections of tuberculin into the tuberculous: (1) In the first stages of tuberculosis, before the formation of sufficient reactional capability on the part of the patient. (2) In the end stage of tuberculosis, especially in older children; an indication that their reactive powers are used up. (3) In some cachectic states e. g., diabetes or carcinoma, again indicating a loss of reactive power and meaning the same as the former. (4) In the course of measles. So far the non-appearance of a reaction in this condition has not been explained; in the course of scarlet fever, on the other hand, the reaction to a tuberculin injection in a tuberculous patient is even more marked. (5) In the course of a series of treatments with tuberculin, meaning probably that the antibodies are saturated.

A drug exanthem, however, resulting from a dose of iodoform or of antipyrin can not be compared or likened to one resulting from a tuberculin injection, for they are due to the action of two altogether different stimuli. The one is a protein while the other is a definite chemical compound. So far the only instance in which immunity, a closely allied condition, has been attained by non-protein substances is in some work recently done by Ford[12]. Experimenting with the poisonous mushroom, *Amanita phalloides,* he has been able to extract a protein-free hemolysin, which is a definite glucosid, and to which animals may be immunized so that 1 c. c. of a 1 to 1000 solution will neutralize one hemolytic unit.

We grant that certain people are very susceptible to the exhibition of some drugs, but it is a long step to call such a susceptibility an anaphylaxis. Further work by means of experiments better planned and more closely controlled than those of Bruck and Klausner must be done before the anaphylactic nature of the reaction, which may follow injections of none-protein substances, can be considered established. The autopsy findings in all of Bruck's, Klausner's, and my guinea pigs were invariably negative, especially as to the emphysematous, non-collapsible condition of the lungs which is one of the especial features of the condition. Moreover, lethal doses of the drugs, such as were generally employed by Bruck and Klausner, and by me in my first series of experiments, should not be used, even in passive anaphylaxis. As has been said before, if there is anything in the reaction, it will be interesting to find out the part taken by each ion of the chemical in the resultant effect.

## SUMMARY.

1. Anaphylaxis is an acute disturbance of metabolic activities of vital cells and may be brought on by the second injection of a protein, after a suitable incubation period following the first injection of the same protein. Proteins are required, though leucin and tyrosin appear unable to cause the reaction.

2. Anaphylaxis and anti-anaphylaxis or immunity are closely correlated conditions, as antiphylactic antibodies can be passively transferred in the blood serum of an animal, affected with either condition, to another animal.

3. Ford has lately been able to immunize animals to a hemolytic glucosid derived from the poisonous mushroom, *Amanita phalloides*. This is the first instance in which a substance outside the proteins has been successfully used.

4. As shown by von Pirquet and others, the reaction of a tuberculous organism to an injection of tuberculin is an anaphylactic phenomenon. There may be rise of temperature, malaise and even generalised skin eruption. Bruck, Klausner and others have been able to passively transfer this hypersusceptibility to guinea pigs so that the pigs will react to a following injection of tuberculin, given in from 24 to 48 hours, with typical anaphylactic symptoms.

5. Bruck thinks that skin eruptions due to the exhibition of drugs with definite chemical formulae are anaphylactic phenomena. He was able to passively transfer such hypersusceptibility from a man with an iodoform rash and from a man with an antipyrin rash to guinea pigs, so that the pigs reacted 24 hours later, on injection of the corresponding drug, with marked anaphylactic symptoms. In the latter case the man had such marked susceptibility to antipyrin that he had taken none for 16 years.

6. Klausner working with a case of iodoform eruption and with several cases of potassium iodid eruptions also found that a passive transference of this hypersusceptibility to guinea pigs was possible. The pigs reacted to injection of the drug causing the susceptibility with anaphylactic shock. Normals of both men showed nothing. The investigations of both workers, how-

ever, should have been more carefully controlled, more animals used, and toxic doses of the drugs should not have been employed. Solutions also should not be too strongly hypertonic, because of the resulting edema at the site of injection.

7. We have made the following investigations. In a man with an erythematous, pustular, potassium iodid rash, the blood was twice removed and serum injected into series of guinea pigs. Likewise another man with a petechial potassium iodid rash gave serum which was used to sensitize pigs. And the opportunity was given to employ the serum of a non-susceptible man who had been taking potassium iodid 2.0 gm. three times a day for six months. In the first series of investigations lethal, hypertonic doses of potassium iodid were employed for injecting the animals and consequently the results are of little value. After my first series a non-lethal, weakly hypertonic dose was used. Plenty of animals were employed both for injections and for controls. Control serum was always human. The ionic action of different metals was also tested.

8. Two at any rate and possibly four or five of my animals, following the exhibition of the drugs, died in an acute manner that is quite unexplainable. The two most acute cases were in carefully controlled animals in which a weakly hypertonic, non-lethal dose of the drug was employed. Control animals showed no such symptoms. Too few pigs were used to draw conclusions as to ionic action of sodium instead of potassium.

9. In a man with an explosive, morbilliform, copaiba rash there was no success in the passive transference of the susceptibility.

10. The results indicate that idiosyncrasy to potassium iodid can be passively transferred by serum; but the propriety of calling this phenomenon anaphylaxis is doubtful.

Only further carefully controlled investigations, with the use of non-lethal doses of drugs for injections, can show the relation of drug exanthemata to anaphylaxis.

All investigations on patients were made on Dr. W. T. Corlett's service at Lakeside Hospital, and I am under obligations to him and to Drs. Torald Sollmann, W. T. Howard and O. T. Schultz for many suggestions. Dr. H. O. Ruh collected all blood used in the experiments.

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# Von Recklinghausen's Disease, with Report of Four Cases.

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The earliest cases of multiple nerve tumors were described by Monttegia Descott[7] about 1813, though Tilesins described the first one in 1793 and Odier, in 1803, had already given the name "Neurom" to the tumors of the nerves. In 1847, Bruch suggested that the tumors were due to polypoid growth of the neurilemma of the nerve while R. N. Smith[6] in 1849 gave a gross anatomic description of the condition. Virchow in 1863 described the condition at some length, dividing the tumors into true, mixed and false neuromata according as they were made up mostly of nerves, fibrous tissue or a mixture of the two. P. Bruns[2] in 1870, described four peculiar cases of his own and also reported four others from the literature, the earliest being that of Verneuil's in 1857. These cases were notable on account of one or more subcutaneous tumors of variable size, made up of convoluted, branched, irregular cords of nerves. Verneuil had already given them the name of plexiform neuromata but Bruns preferred to designate them," "Ranken-neurom" or, as they resembled varicocele to the touch, "neuroma cirsoideum." The favorite location of these tumors was on the face, neck or sacral region, they were quite vascular and contained an abundant lymphatic supply, one of these cases resembling an elephantiasis. There was also a profuse discharge of lymph on cutting into the tumors, as we too have found in several of our cases. A number of the authors already quoted had noted like conditions and, in addition, the presence of pigmented areas of the skin, multiple skin tumors, functional disturbances, etc. It remained for von Recklinghausen[14] to compile the several findings and establish the condition as a definite clinical entity. As a result of his researches, he concluded that the tumors arose from the endo- and perineurium of the nerves, as well as from the connective tissue of small vessels and glands, consequently the condition was a true fibromatosis and he named it neurofibromatosis.

Prudden[13] in 1880 and Hektoen and Preble in 1901, among American authors, have studied the disease thoroughly in connection with cases of their own and others taken from the literature.

During the past 10 years at Lakeside Hospital there have been five true cases of the disease, but as the records of one have been unfortunately lost, only four of them will be reviewed.

*Case I.* Clinical summary: Multiple subcutaneous tumors, soft, freely movable, painful, bluish-violet, nodular; nerves passing to tumors demonstrated at operation; no elephantiasis; cutaneous pigmentary changes; nevi; average mentality; no hereditary history.

The patient, J. G., machinist, alcoholic, age 67, born in the United States, married, no children, weight 140 pounds, was treated in the Lakeside Hospital Medical Dispensary for several months before admission on the Medical Service of the Lakeside Hospital, July 14, 1904. Was operated upon by Dr. Crile, July 26, 1904, and discharged August 23, 1904. (L. H. M. S. No. 4217, L. H. S. S. No. 5189.)

Family history: Father and mother died of pleurisy and typhoid respectively. Had three brothers and three sisters all living and well. No history of painful subcutaneous tumors nor of elephantiasis formations.

Past history: Has had a number of attacks of bronchitis and has been troubled with pain in the upper thorax. Hearing poor.

Present history: For eight years preceding admission has been having pains all over his body but now especially about the left shoulder and back. These pains have been gradually increasing since their onset and are worse in bad and changeable weather. Occasionally severe attacks of pain have prevented him working at his trade. There are a number of soft subcutaneous tumors over the body, which have been present for a number of years. All of them but the one near the elbow on the right arm are tender, especially in rainy weather.

Physical examination: A small, nervous, shaky man with a wrinkled, scaly skin which is darkly pigmented in places. Axillary lymphatic glands enlarged. Chest hyperresonant. Has bilateral, reducible, inguinal herniae. Scar back of corona glandis.

Scattered over the body are numerous subcutaneous tumors, which vary in size from .5 cm. to 3 cm. in diameter. Some are flattened while others are spherical. Some are soft, others hard and resistant. The majority are small, bluish in color and are present in the greatest numbers over the chest. Nevi are numerous.

In the right posterior cervical triangle are three small, soft, slightly raised, rounded, subcutaneous tumors. Near them and just above the middle of the clavicle is a larger, similar tumor measuring 2 cm. by 1.5 cm. This is painful when handled.

On the left side of the neck is a tender growth measuring 1 x 1.5 cm. situated just behind the middle of the sternocleidomastoid muscle. The skin over it is movable while the tumor itself seems fixed at its base. Other smaller subcutaneous tumors are present in the left posterior triangle of the neck.

On the right shoulder is a solitary, tender, spherical tumor 3 x 4 cm. situated between the outer part of the clavicle and the head of the humerus.

A small but very distinct tumor 1.5 x 1 cm. is present 7 cm. above the internal condyle of the right humerus. Not very painful.

On the upper outer surface of the left arm, anterior to and just above the deltoid insertion is another large, spherical, soft, slightly tender tumor measuring 2 x 3 cm.

The only large tumor on the lower extremities is an irregular, soft, elongated rather tender one, measuring 2.5 x 1.5 cm., lying on the quadriceps extensor muscle of the left thigh about half way between the hip and the knee.

A single, soft, not painful, not tender, multinodular tumor is situated on the anterior surface of the right forearm 6 cm.

below the crease of the elbow joint. Patient referred its origin to a strain in his boyhood.

At the time of operation, all these tumors except the last were found encased in a fairly definite capsule and, with the same exception, nerve fibers were found running to all of them. All the tumors were removed without any difficulty. A slight amount of clear fluid was found when the second one was opened. The last one described above had no definite capsule and microscopically appeared to be a lipoma.

Pathological summary: Microscopical examination showed dense fibrous tissue in all the specimens except the last described, which was a pure lipoma. The presence of nerve tissue in the tumors was not mentioned.

*Case 2.* Clinical summary: Multiple cutaneous and subcutaneous tumors, soft, freely movable, not painful, not tender, violet or gray in color. Plexiform neuromata in left scapular region and about neck. Large fibroma, with elephantiasis formation, attached to the sternum and chest anteriorly and increasing in size laterally. There is a serosanguineous discharge from this growth. Dark blotchy, cutaneous pigmentary changes; nevi; average mentality; history of similar multiple cutaneous tumors in mother and four sisters.

Pathological summary: One tumor taken from the back is a neurofibroma, the other an ordinary lymphendothelioma. Large tumor of the chest and abdomen is a fibroma with increased vascular supply and numerous lymph spaces—*neuroma lymphangiectatica.*

The patient, G. S., machinist and foreman, age 40, born in the United States, married, has five children all of whom are free from subcutaneous tumors. Entered the Lakeside Hospital Nov. 27, 1910, complaining of a large suppurating tumor attached to the sternum, and multiple small subcutaneous growths all over the body. Referred by Dr. H. S. Rhu of Marion, Ohio, to Dr. G. W. Crile. Discharged Dec. 12, 1910. (L. H. P. W. S. No. 5759.) The measurements were made Dec. 5, 1910, and the photographs (Figs. 1 and 2) during December, 1910.

Family history: Father died at age of 55 of intestinal trouble. Mother, who is still living, had a round, painless tumor removed from her arm near the wrist years ago. This growth never recurred. No multiple subcutaneous tumors. Four sisters of the patient are living, all of whom have multiple skin tumors of small size but no large ones. As far as is known, no other members of the family have subcutaneous tumors. Negative history of malignancy, tuberculosis, insanity and epilepsy.

Past history: Except for the usual diseases of childhood, patient has always been well. When 12 years of age, he was thrown from a wagon and was injured, since which time his spine has been markedly deformed.

Present history: During boyhood patient first noticed multiple subcutaneous tumors scattered thickly all over his body but especially over the chest and upper arms. These have gradually increased in size since they were first discovered until at the present time they vary from 0.5 cm. to 4 cm. in diameter. None of them have ever been tender or painful. According to the statement of the patient's mother, he had a small, soft, subcutaneous tumor over the lower portion of the gladiolus at birth, while the patient himself first noticed it when he was five years old. It grew slowly in size until two years ago it was about the size of his fist and caused him no pain or distressing symptoms of any kind. Since then it has increased rapidly in size, especially a lateral extension over the left chest, which is entirely of recent growth. Six months before admission it became red, tense, tender and of such a size and weight that he was unable to work. Several weeks before coming into the hospital the tumor was incised and a considerable amount of serosanguineous fluid mixed with blood clots was removed. Even since then there has been a slight discharge from this incision which on bacteriological examination showed a mixed infection with a predominance of *Staphylococcus aureus*. The dark pigmented cutaneous areas have been present for years. Recently the patient has been losing in weight.

Physical examination: Patient is a small anemic man with a slight scoliosis, a marked dorsal kyphosis and a corresponding lumbar lordosis. The lymphatic glands are all palpable but not greatly enlarged. No abnormalities in the eyes, ears, nose, throat, circulation, abdomen, extremities or reflexes. The skin is soft and loose, and nevi and dark pigmented areas are numerous. Thickly scattered over the entire body, but especially on the chest, back, neck and arms are numerous small subcutaneous tumors ranging in size from .5 cm. to 4 cm. in diameter. The smaller ones are red, firm, neither tender nor painful, and while attached to the skin and the subcutaneous tissues they are movable on the deeper structures. The smaller cutaneous ones are bluish, opalescent, soft, not tender, not painful, not inflamed, almost fluctuant and do not change color on pressure.

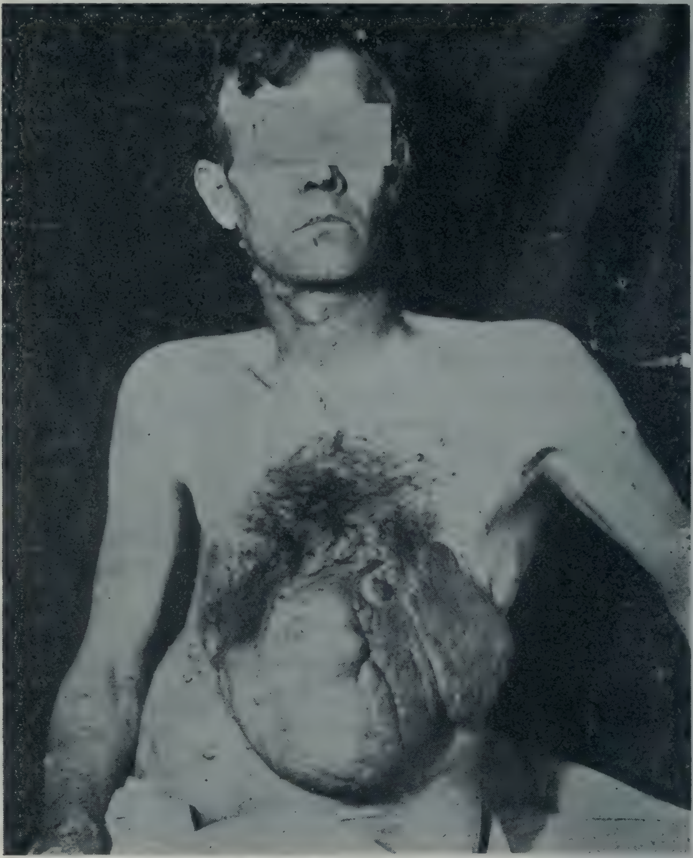

Fig. 1. Patient No. 2. Large neurinoma of chest, dating from birth.

One tumor on the back over the left scapula and several on the neck are flattened, elongated, not tender, not painful, movable on the deeper tissues, with the skin movable over them and on palpation have a feeling similar to that of a varicocele.

Over the lower sternum and chest anteriorly and apparently closely attached to them, is a large, pedunculated, lobulated, rather firm tumor with areas of softening, having a base measuring 16.5 cm. vertically and 35.5 cm. transversely. The upper border is in the fourth interspace in the right sternal line while

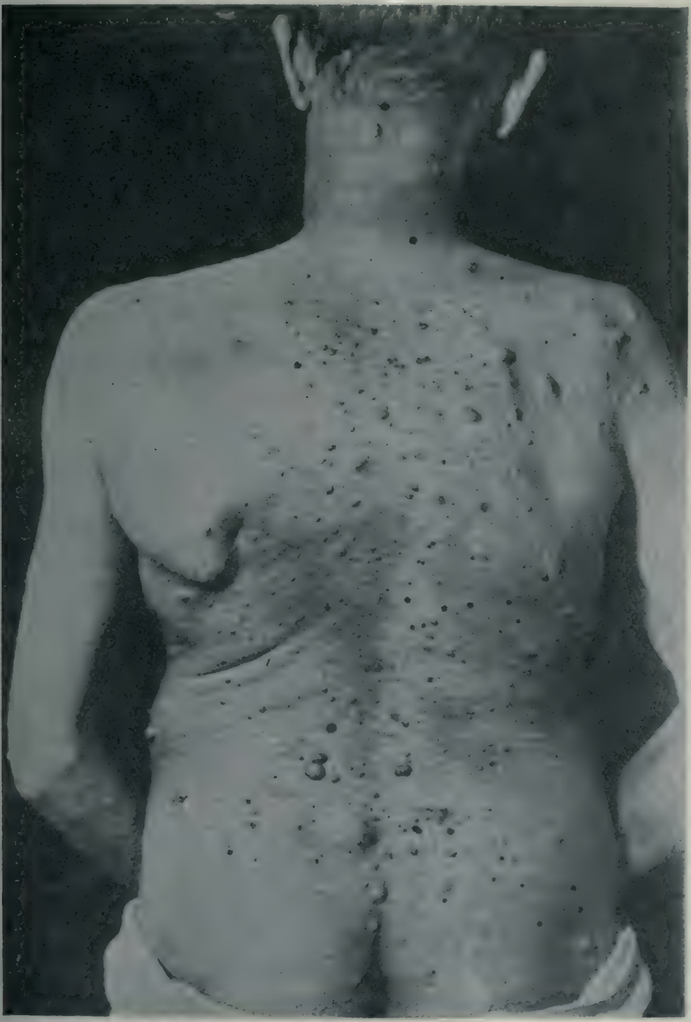

Fig. 2. Patient No. 2. Large Ranken-neurom of left scapular region and numerous small subcutaneous tumors.

the lower edge is 2 cm. above the umbilicus. With this as a base, the tumor hangs dependent over the upper abdomen with shallow creases dividing it into three more or less distinct lobules. When the patient is in the dorsal position the highest point of the tumor is 10 cm. above the level of the umbilicus.

The oldest lobule, which lies to the right, is somewhat firm, irregular in outline, nodular and measures over its surface vertically 29.5 cm. The skin covering it, other than being closely attached, is similar to that covering the rest of the body. From an old incision near its upper border, a thin seropurulent discharge is escaping. Evidence of inflammation and of degeneration are seen about this opening.

The middle and left lobules are firmer and less dependent than the original tumor. The skin over them is tough, closely attached, and of a dark rose-red color. At the greatest part they measure 15.5 cm. vertically.

Subsequent history: Six months after leaving the hospital the patient was working steadily and the incision in the large elephantiasis formation was closed.

Pathology: The tumor of the back measured about 1.5 x 2 cm. x 1.5 cm. and the consistency was only moderate, the tumor appearing to be quite vascular. Microscopically there is a moderately well defined fibroma extending up as far as the middle layer of the corium. The nuclei stain quite deeply and are numerous. The tumor is vascular and there are many primary lymph spaces, having no endothelial linings, between the tissues. At the epidermal border there is a large sebaceous cyst along the hair. Only one small nerve is seen and the axis cylinders appear quite normal, though the nuclei of the sheath of Schwann are increased in number, appearing like the nuclei of fibrous tissue. The nerve is well defined.

A second tumor removed from the back was of like size and consistency. Microscopically the tumor shows a growth made up entirely of hyperplastic lymph endothelium. There are numerous large lymph spaces just below the epidermis lined with strands of endothelial cells while the base of the growth is a solid mass of the same cells. The growth is quite well defined.

Section removed from the large tumor of the sternal region measures 2 x 1 x 3 cm. and is rather grayish white in color. Microscopically the tissue is made up entirely of a moderately vascular fibroma, containing some blood vessels and lymph spaces. The nuclei are quite numerous, variable in size and appear to have no definite direction. There is a moderate infiltration with small round cells and occasional mast cells, especially around the blood vessels. No nerve tissue is seen. The tumor is not well defined and gradually merges into the corium and epidermis.

Another biopsy made about six inches from the former one was about the same color and consistency. Upon microscopical examination there is a marked increase in the number of nuclei. The lymph spaces are also more definite and lined with endothelial cells while deep in the section are found two large irregularly shaped blood spaces with merely an endothelial lining. Near the center of the section a small nerve made up of about ten axis cylinders is seen. It appears to be normal and there is no increase in the nuclei of the sheath of Schwann.

*Case 3.* Clinical summary: Multiple cutaneous and subcutaneous tumors, soft, movable, not tender or painful; plexiform neuroma and elephantiasis formation on cheek, likewise neither tender nor painful, and from which much serum and blood exuded at the time of operation; many large and small dark cutaneous pigmentations, hypertrophy of right maxillary bones; average mentality; no hereditary history.

Pathological summary: Of two small tumors from the back, one was a neurofibroma and the other a pure fibroma. The tumor of the cheek showed dense fibrous tissue and intermingling nerves.

The patient, C. W., farmer, age 21, American, single, weight 150 pounds, entered the Lakeside Hospital Jan. 20, 1911, complaining of a large disfiguring tumor of the right cheek. A plastic operation was done by Dr. W. E. Lower, Jan. 23, 1911, and patient was discharged March 7, 1911. Second admission on April 7, 1911, patient complaining of severe abdominal pain for which an appendectomy was done and patient discharged April 21, 1911. Photograph (Fig. 3) taken Jan. 21, 1911. (L. H. S. S. No. 17618 and No. 17876.)

Family history is entirely negative as to mental disturbance or a like disease. Patient's past health has always been good. The large dependent growth on right cheek was first noticed shortly after birth. Since then it has gradually increased in size along with the rest of the body. There has never been any local pain, discharge or variation in size. As far as the patient knows the multiple cutaneous tumors have been present over the body since birth and they have never given any pain. The pigmented spots have also been present as long as he can remember.

Physical examination: Patient is a well developed, well nourished man. No abnormalities in pupils, ears, circulatory system, or gastro-intestinal tract. Cervical glands are enlarged. Expansion of the lungs is limited on the right. Reflexes are active.

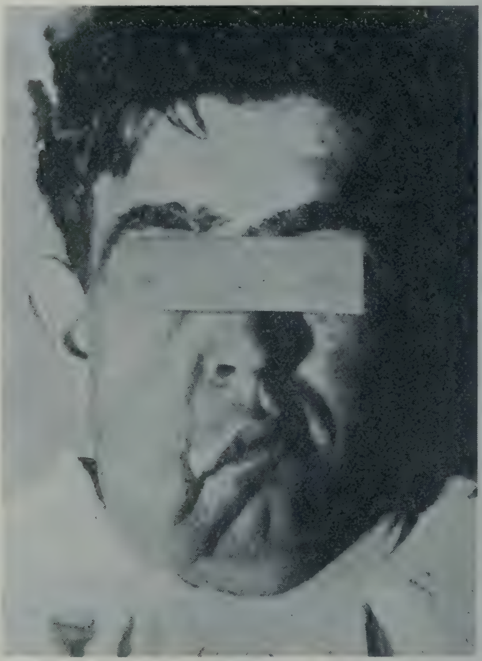

Fig. 3. Patient No. 3. Large Ranken-neurom of the right cheek. Numerous subcutaneous tumors.

The skin is covered with small, dark brown, pigmented areas of variable size. Scattered closely over the trunk and extremities are numerous, small, soft, slightly raised, faintly purple colored, cyst-like tumors measuring .5 to 1 cm. in diameter. Artificial light at an angle gives the skin a peculiar mottled appearance. A few firmer, larger, subcutaneous tumors are also present. On the right of the face is a large, thick growth measuring 19 x 16 cm. and hanging down below the lower edge of the inferior maxilla. It involves the entire right cheek and right halves of both upper and lower lips. By the tumor's weight the right angle of the mouth is drawn well down and there is a slight ectropion of the right lower lid. The skin covering the tumor is dark, heavy, thick and freely movable. On palpation of the growth a definite tender tumor mass is felt with a general, soft, diffuse structure and consistency not unlike a varicocele. The mucous membrane lining the right cheek is light red in color, soft and hypertrophied, so that a small pedunculated mass 4 x 5 cm. hangs opposite the molar teeth. Both the superior and inferior right maxillae are thicker than those on the left, as demonstrated by the x-ray.

Hemorrhage and escape of serum was very marked at the time of operation and there was an intense postoperative edema of the parts which lasted for several days. At first patient did not react very well from the operation.

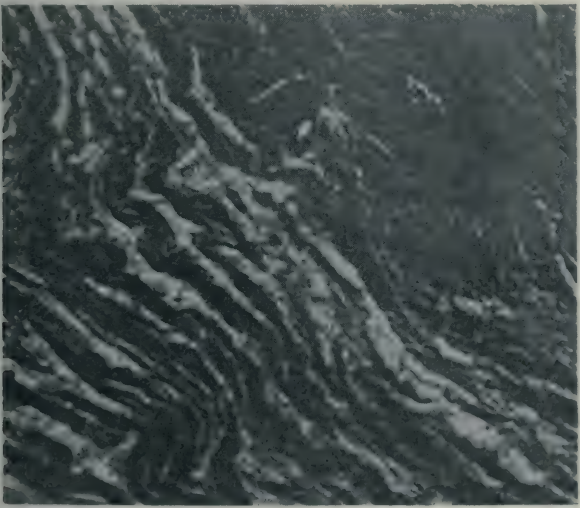

Fig. 4. Section of subcutaneous tumor from Patient No. 3. Two well defined nerves in a fibrous tissue growth. Increase in fibrous tissue nuclei. Axis cylinders of nerves made out of with a slight increase in the number of the nuclei of the sheath of Schwann. These photomicrographs were all taken with a No. 4 eyepiece and a No. 3 nosepiece, with a bellows length of 18 cm., giving a uniform magnification of X 100.

Subsequent history: Patient was readmitted one month later with severe pain and tenderness in the right iliac region, and an appendectomy was done. At this time there were no changes noted in the skin and the right cheek presented an excellent cosmetic result from the plastic operation.

Pathology: A tumor removed from the chest, 2 x 2 x 2 cm., was of moderate consistency and grayish in color. Microscopically the tissue is a quite well defined fibroma (Fig. 4), showing in different sections from 12 to 18 different nerves of varying size. These nerves appear to be normal except for a moderate increase in the number of the nuclei of the sheath of Schwann. In some places the fibrous tissue has grown in between the axis cylinders, forcing them apart. Lymph spaces are very numerous, especially around the borders of the tumor. There also appears to be a secondary increase in the fibrous tissue of the vessel walls.

In a like tumor removed from the back a pure fibroma, with nothing not already described, was found.

The tissue from the cheek was a section 1 x 4 x 2.5 cm., whitish in color and of good consistency. Microscopically the entire tumor is made up of dense fibrous tissue, the fibers running in different directions. In some places the nuclei, flattened out and closely packed together, are seen in cross section; while again they are found in longitudinal section. Vessels are numerous and many lymph spaces with endothelial lining are seen. Several large nerves are present and they are not well defined, as in all our other tumors examined, but appear to gradually merge into the surrounding fibrous tissue. The nuclei of the sheath of Schwann are greatly increased in number but it is impossible to differentiate them from the nuclei of the fibrous tissue.

*Case 4.* Clinical summary: Several freely movable, slightly painful, not tender, subcutaneous tumors; Ranken-neurom of face with dark pigmentations and heavy growth of hair over it. Cutaneous pigmentary changes, average mentality and no hereditary history. Free escape of blood and serum at time of operation, marked postoperative edema and recurrence of growth following operation.

Pathological summary: Plexiform neurofibroma with hyaline degeneration of the muscle fibers and formation of lymph spaces.

The patient, C. S., clerk, American, single, aged 17, weight about 125 pounds, entered the Lakeside Hospital May 28, 1909, and was discharged June 9, 1909. Patient of Dr. D. P. Allen (L. H. S. S. No. 10317). Readmitted May 2, 1911, and discharged May 19, 1911; patient of Dr. G. W. Crile (L. H. S. S. No. 18018).

Family history: Patient's mother died with neuritis but otherwise there is nothing suggestive in the family history. The patient had a fracture of his skull in his second year of life but was otherwise always well. He states that shortly after the fracture of his skull, a mass was first noticed over the temple and right forehead. It grew gradually in size so that in youth it hung well over his right eye and obstructed his vision upwards. Four months previous to his first admission he began to have frontal headaches, chiefly on the right side. At the same time the tumor would become painful and throb. When he was 11 years old a stiff, heavy growth of hair, blending with the scalp, appeared on the upper part of his right cheek and forehead. Two tumors present in the right temporoparietal region were also first noticed soon after the cranial fracture. These have never been painful or tender and have remained stationary in size. He does not remember when the tumor near his right elbow first appeared, but it has never been painful. Dark pigmentations over the elephantiasis formation on the face and cutaneous blotches elsewhere have been present for years.

Physical examination: Normally developed, healthy appearing boy. Situated in the right frontal and temporal region is a tumor mass 7 x 3 x 1 cm., of doughy consistency. It is of such a size that it causes the right eyebrow to droop down over the right upper lid. It is not sensitive, not swollen or red and it does not fluctuate. On palpation it feels much like a bundle of worms, and within the tumor is a small, slightly tender mass about 1 cm. in diameter. The skin over the growth is closely attached, deeply pigmented and covered with stiff hair. This pigmentation and the growth of hair continues down over the skin covering the right cheek. Posterior to this tumor, in the right temporal region, is a softer, more movable, flattened, subcutaneous mass measuring 4 x 3 x 1 cm. And just behind this last one, in the right parietal region, is another similar tumor. The skin over both is deeply pigmented and covered with a heavy growth of hair. Neither mass is tender or painful. The only other tumor is a subcutaneous growth found at the flexure of the right elbow. It is movable, soft, elongated 1 x 2 cm. and is not sensitive.

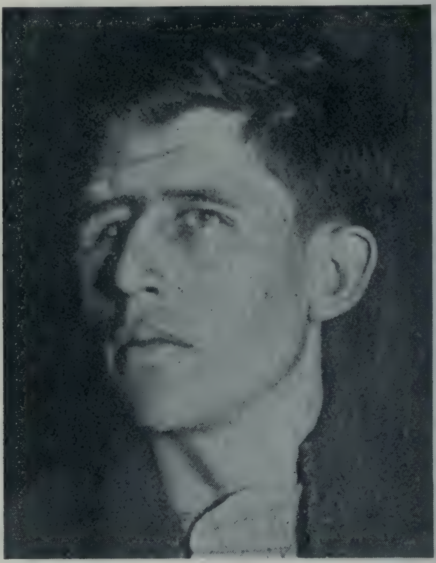

Fig. 5 Patient No. 4 Ranken-neurom of right eye-brow and temporofrontal region.

The first operation was performed by Dr. D. P. Allen, May 29, 1909. By this plastic operation a mass of tissue 6 x 2 x 1 cm. was removed from the side of the head with excellent cosmetic results. Hemorrhage was free, as was also the flow of serum.

Subsequent history: One year after he was discharged he noticed that a soft subcutaneous tumor was growing on the right forehead in the region occupied by the former growth. It was never painful or sensitive and the pigmentation of the skin remained the same, though the hair covering it turned gray. On readmission May 2, 1911, this tumor measured 8 x 3 x 1 cm. A second plastic operation was done by Dr. G. W. Crile May

3, 1911. As in other operations on this type of tumor the hemorrhage was free and escape of serum marked. Patient reacted well to operation and was discharged much improved.

Pathology: A section 3 x 2 x 2 cm. was taken from a large mass 8 x 3 x 1 cm. removed from the forehead. The tissue is soft, grayish in color and feels as if a bundle of cords was present within it.

Microscopically there is a fairly well defined tumor made up in places of almost successive, circling strands of fibrous tissue, between are found primary lymph spaces containing coagulated lymph (Figs. 6 and 7). In some areas the spaces are found to have endothelial cells lining them. There are five large nerves in the portion of tissue examined. These show normal axis cylinders and a moderate increase in the number of the nuclei of the sheath of Schwann. The nerves are very well defined by their perineurium from the surrounding structures. Numerous bands of muscle fibers are present, showing all grades of hyaline degeneration. The fibers are forced apart

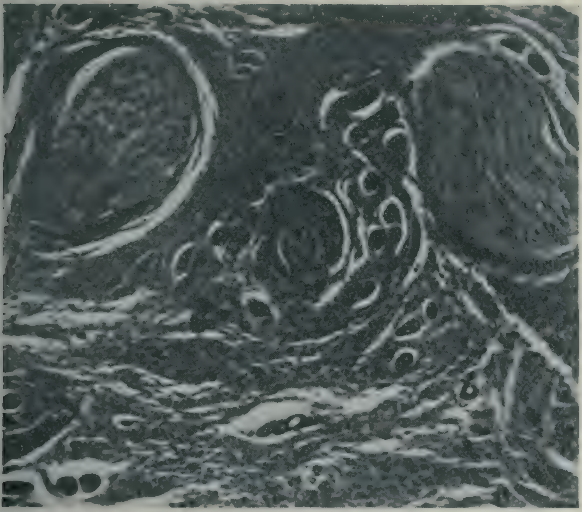

Fig. 6. Section from Ranken-neurom of face of patient No. 4. Three well defined nerves are seen in a fibrous tissue overgrowth. Small areas of hyaline degeneration of muscle, with fibrous tissue growing between them, are present.

by the growth of fibrous tissue, have lost their nutritional supply and, as a result have degenerated, as is shown in the photomicrograph (Fig. 6).

From a summary of the case reports and a short résumé of the condition already given, one finds that the most marked symptoms of the disease are the multiple cutaneous tumors, the pigmentary anomalies, the tumors of the nerves and the elephantiasis formation. Still another change should also be added to the four already given, viz., functional disturbances. These will be taken up in the order of their frequency.

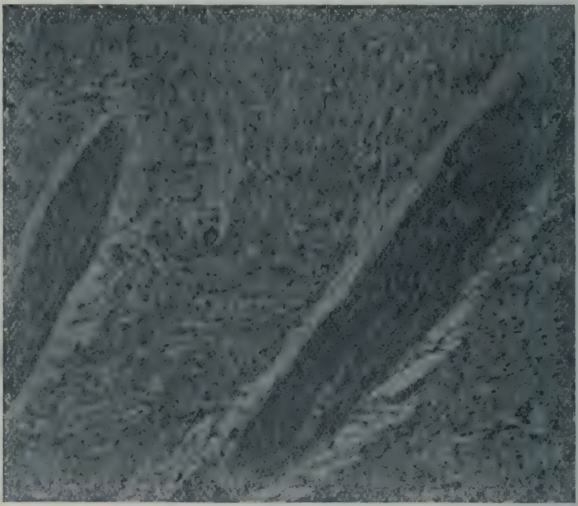

Fig 7. Section taken from same tumor of patient No. 4. Primary lymph spaces between strands of fibrous tissue. The lower portion of the mass is a solid fibrous tissue overgrowth.

The cutaneous tumors, going under the names of multiple fibromata, fibroma molluscum, neurofibroma, etc., vary in size, shape, number and position. As a general rule, the tumors are found more on the anterior and posterior parts of the trunk, especially on parts subjected to pressure, though they may be found anywhere, even on mucous membranes, as in one of our cases. Their number may run from a single tumor up to several thousands, thus Modrenjenski's[7] patient had 3000. One of our patients also had a large number and there may be so many that it is impossible to count them. Their size is quite variable: they may be as small as a pinhead or as large as a man's fist. Generally, however, the ordinary cutaneous tumors vary from the size of a chestnut to that of a walnut. The growths may be elevated or depressed; they are generally of a pinkish or faint bluish color; and to the touch they feel like small lipomata. Generally they are not tender, though, as in several of our cases, patients complain of pain in the tumors—supposed to be due to pressure or traction on the small nerves frequently found within them. In fact Soldan[16] believes that at some time they all contain at least a "Stämmchen" from which the fibroma, of which the tumors are made up, has originated, and that then, perhaps, there has resulted an atrophy of the nerves leaving the pure fibroma. We might say here that in none of our cases was any noticeable atrophy of nerves noted, though it has been seen by some workers.

The tumors may be present at birth or appear later, as at puberty; while pregnancy at times appears to exert an influence on their number and rate of growth. Thus, Hirst's[8] patient, aged 18, had four typical growths on the anterior surface of the body, while during pregnancy there was an increase not only in their size but also in their number. Trauma at times appears also to cause an increase in their rate of growth.

The next most common symptom of the disease is pigmentary change. It is present in at least 25% of the cases and generally even more frequently. The pigmentary spots are generally dark brown in color and, varying in size and shape, appear to have no connection with nerves. The entire pigment layer of the skin may be more strongly developed than normally, though histological examination shows nothing abnormal in its development, merely an increase in the chromatophore cells of the pigment layer of the epidermis and upper corium. Hemangiomata may be present, as in one of our cases, and pigmented moles are frequently seen.

A less frequent occurrence in connection with the disease is the presence of tumors of the nerves. The tumors may be single and appear but as a local enlargement or there may be a diffuse enlargement of the entire nerve. Again the nerve may coil up and branch as in an amputation stump (Ranken-neurom, plexiform neuroma, neuroma cirsoideum). In connection with these last tumors, they may involve a deeper nerve or nerves or they may be rather superficial, forming a "lappiger" tumor as in our cases Nos. 3 and 4, somewhat resembling a lipoma. On palpation they are rather soft and their contents feel like a bundle of earthworms or a varicocele and frequently they tend to the elephantiasis condition to be mentioned later. Thus Czerny[3], reports a girl with a large, soft, irregularly lobulated growth about the size of a large watermelon attached to her lumbosacral region. It was present from birth but increased in size. The contents were fibrous tissue, a plexiform neuroma and large lymph spaces. Three generations in the girl's family were .affected with a like trouble. The "Ranken-neurom" is most frequently found on the face and neck when superficial, especially along the eyebrows as in our two cases or along the side of the cheek and head. .Of the internal nerves affected with this variety the sciatic is probably most often involved.

Of the ordinary tumor involvement of nerves the vagus is probably most often affected, then come the abdominal sympathetics and the sciatics. Often the vagi at postmortem appear like a string of beads from the numerous small neuromata studding them. Some cases may have several hundred tumors on the vagi alone. These nerve tumors may grow to be of large size, thus Hektoen and Preble[7] speak of a case with a neuroma 1 x 3.5 cm. and several cases have been reported in which a neuroma the size of a child's head was found in the pelvis. Often the tumors appear to cause no discomfort except from pressure, while again there may be abdominal pain, tachycardia, pain in the limbs, etc.

It may be well to mention in this connection that in quite a few cases coming to autopsy, brain tumors have been found. They have been gliomata, endotheliomata and true neuromata, or better neurinomata. The spinal cord and its spinal nerves are also affected at times. Curiously enough, a true neurinoma of the optic and olfactory nerves has never been found, a point which will be mentioned later.

A symptom of the disease less frequently found, but quite characteristic, is that of elephantiasis. Since the earliest history of the disease it has been noted that quite frequently the patients were also affected with chronic swelling of their lower limbs, genitalia, neck or side of face. Czerny[3], already quoted, and P. Bruns[2] were among the earliest to call especial attention to the symptom. The patient may be troubled for years with a swelling of one or both limbs or of one of the labia, while there is absolutely no circulatory disturbance or filaria infection. On palpation the skin is found to be somewhat thickened and the tissue may feel like a lipoma or somewhat like a bundle of worms from the strands of fibrous tissue running throughout. Quite frequently a plexiform neuroma is found in these formations, especially when on the face and neck. On incising these elephantiasis formations, there is a profuse discharge of lymph, as was especially noted in three of our cases, Nos. 2, 3 and 4, due to opening of dilated lymph channels. Consequently, following operation there is a tendency of the parts after being sutured to swell up from a local collection of serum.

Bruns[2] explains this formation as follows: "Meiner Ansicht nach ist dieselbe eine Erscheinungen der kongenitalen Elephantiasis im weiteren Sinne, wenn wir darunter eine angeborene. Anlage zu geschwulst-förmiger Bindegewebswucherung. zu Fibrombildung enstehen, welche die Haut und Unterhaut betrifft und bald die Blut-gefässe, bald die Lymph-gefässe, bald die Nerven wesentlich beteiligt. (Elephantiasis Telangiectatica, Lymphangiectatica und Neuromatodes)."

In other words, this congenital tendency to fibrous tissue formation affects the lymphatics along with the nerves and blood vessels and there is then a hindrance to the lymph flow and resultant elephantiasis.

The final principal symptoms in connection with this disease are functional disturbances and they are probably common enough to be placed on an equal footing with the other four principal symptoms. Thus of 32 cases reported by Prudden [illegible], there were two cretins, one idiot and two of weak intellect, one cryptorchid and one epispadiac. The patient may or may not complain of pain, though quite frequently patients affected with abdominal neurinoma complain of pains in their stomach or bowels. Large neurinomata may cause an actual disturbance of function, either sensory or motor, and tumors pressing on the vagi may cause palpitation, tachycardia, bradycardia, stomach trouble, etc., though very frequently a patient with a vagus studded with neurinomata will come to autopsy without having had symptoms pointing to the same. There may be paresthesia, anesthesia or weakness. Sometimes paralysis of one of more limbs is present, while in the case of Hektoen and Preble there was arthralgia as well as joint changes and trophic disturbances. Scoliosis has been noted in a few cases and Seefelder[15] has lately called attention to the occasional occurrence of hydrophthalmus in these cases. Congenital defects are sometimes seen and a few of the cases have regular occurrence of chills (Harbitz[5]).

Etiology: All ages are affected with the disease and 65% of them are males. The disease may be either present at birth or it may develop later as at puberty or at the menopause. As already mentioned trauma and pregnancy at times have some influence on it. The disease is both congenital and hereditary, a large percentage of the cases are affected at birth and at least one-fifth show a hereditary tendency. Thus in one of Harbitz' cases nine persons in five consecutive generations were affected: the family could not be traced further back, but it was apparently transmitted through the female members of the family. Czerny's case has already been mentioned. Bad hygienic conditions with a familial tendency may also predispose to the disease. In one of our patients the mother and three sisters were affected.

Prognosis: In this class of cases the outlook is usually good and as a general rule the patients die of some intercurrent infection. In the 32 cases reported by Prudden the average age at death was 31 but this is probably below the general average as these cases were all exceptional examples of the disease; many of them live to a good old age. However, there is one class of patients affected with this disease in which the prognosis is not so good, we refer to the cases affected with the "Ranken-neurom." Quite frequently they return after removal as in our Case 4 and in about 12% of cases there is a following sarcomatous change of the tissue, though our case shows none as yet. In addition, the patients with the elephantiasis form of the disease, such as our Nos. 3 and 4, bear operation rather poorly and the prognosis is far from good. Bruns[2] and Czerny[3] report very poor results in such cases. If possible it is better not to attempt operation if the growth is at all extensive.

Diagnosis: Given a case showing multiple skin tumors, with pigmentations and perhaps an elephantiasis formation the diagnosis is not at all difficult to make. It is in such cases as our No. 4 where the diagnosis is difficult to make and it may perhaps be verified only after a most careful examination with histological methods. Confusion with lipomatosis is probably most liable to give trouble as there are some cases reported where there are multiple localized lipomas with elephantiasis formation and pigmentations, moreover with a history of the familial tendency. Perhaps histological examination would show some of these cases to be true cases of von Recklinghausen's disease but the distinction should be kept in mind and we would refer the reader to the excellent article of Lyons[12] on "Adiposis and Lipomatosis."

Pathology: Since the early part of the last century multiple tumors of the nerves have been known and there has always been a great deal of discussion as to their origin. The view of von Recklinghausen has already been stated, later in 1898 he felt that the tumors should be called fibromas instead of neurofibromas, believing that the essential feature was an overgrowth of the connective tissues of the endo and perineurium and that the term neuroma should be used only for tumors formed of proliferative nerve cells. However, several workers, among them Knauss[10], have described multiple subcutaneous growths of this sort in which numerous ganglion cells were found, and Hook[9] reports his case and 34 others of ganglioneuromata, 10 of them being of the adrenal. In four of these cases there were multiple skin tumors. Certainly these did not arise from connective tissue. Again Generisch[4] and several others have noted a proliferation of the sheath of Schwann but thinking it to be of mesodermal origin have regarded the tumors as essentially fibromatous. However, the excellent work of Kohn[11] and the work of Harrison[8] on the embryos of *Rana esculenta* and *sylvativa* have shown conclusively that the sheath of Schwann is ectodermal in origin. Several workers had already called attention to the fact that the optic and olfactory nerves were devoid of a sheath of Schwann and they have never been found to be affected with a true neurofibromatosis or better neuromatosis. Therefore Verocay[17] has lately come to the conclusion that the growths are derived either from the cells of the sheath of Schwann or from the less differentiated precursors of the same. Consequently the tumors derived from these imperfect neurons should be termed "neurinoma," and at the same time with the overgrowth of the neurogenous tissue there may be an overgrowth of fibrous tissue as is found in connection with scirrhous cancer. Also, there may be an accompanying serous infiltration and edema passing into an elephantiasis formation as was seen in our cases. Though it seems quite probable too that Bruns'[2] explanation is correct; that the fibrous tissue overgrowth may obstruct the lymph flow and cause the accumulation of fluid in the tumors.

Thus far in our cases we have been unable to find any such stain or stains which would enable us to differentiate the nuclei of the connective tissue from those of the sheath of Schwann. Certainly, however, there appeared to be an increase in the number of the nuclei of Schwann's layer, but in no case were any ganglion cells found. In all but one of the cases the nerve tissue was clearly defined and appeared to be normal. In our last case, however, the nerves were not sharply demarcated from the surrounding fibrous tissue but appeared to be a part of the same, and it was impossible to distinguish the nuclei of Schwann's layer from the nuclei of fibrous tissue. This requires further study and we hope to go into the pathology more extensively in the future.

Treatment: Of this little need be said as it all depends on the case and how affected. As in our case No. 1 the small tumors may be excised because of pain. The "lappiger" tumors of the face and neck are the ones most often calling for surgical attention and it may require several operations before sufficient tissue is removed. But as has been shown in our case No. 4 there is a frequent chance of their recurrence and 12% of the Ranken-neuromata undergo sarcomatous change. The patients with the large elephantiasis variety bear operation very poorly and interference is to be discouraged.

## SUMMARY.

In four cases of von Recklinghausen's disease, occurring at the Lakeside Hospital in the past 10 years, three patients had multiple cutaneous tumors and pigmentations; while in three of them large Ranken-neuromata, two of the face and one of the back were found. In one patient an immense neuroma lymphangiectatica of the sternum was present. No especial functional disturbances were noted except pain in the cutaneous nodules in one of the cases and severe frontal headaches in another.

In two of the cases the tumors were congenital, in another the growths were present for years; while in another trauma at the age of two years was given as the cause of the growth. Heredity was present in but one case, the patient's mother and three sisters being affected to his knowledge.

Recurrence of a Ranken-neurom of the face, following operation was found in one case, but there was no sarcomatous change as is found in 12% of such cases.

In three of the cases histological examination revealed fibromata with enclosed nerves; while in the other patient the tumors were cut from nerves at the time of examination, though nothing was said of nerve tissue in the histological description of the sections.

It was impossible to corroborate Verocay's findings that the tumors arise from the sheath of Schwann or its precursor neurons and therefore should be called neurinoma. However, in one case the nerves were not well defined from the surrounding fibrous tissue and there was a marked increase in the nuclei of the sheath of Schwann.

In conclusion the writers wish to express their great indebtedness to Dr. O. T. Schultz of the Department of Pathology of Western Reserve University for his many suggestions and for the taking of the photomicrographs. We also wish to thank the physicians already mentioned for the use of their cases.

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No. 23

# Hemorrhagic Infarction of the Adrenals, With Report of a Case.

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(From the Pathological Laboratory of the Lakeside Hospital.)

Although much attention has been paid to infarction of the various other viscera, the occurrence of infarction of the adrenal glands has received but the scantest attention. The purpose of this article is to point out again that such lesions do occur and to report a case illustrating the condition.

The patient, a man of forty years, a sign-painter by trade, was admitted to the wards of the Lakeside Hospital, Cleveland, January 29, 1910, on the service of Dr. C. F. Hoover. He complained of pain in the right chest, shortness of breath and a feeling of extreme weariness; duration two days. His temperature was 102.5°, pulse 120, respirations 35.

*Family History*: Negative.

*Personal History*: The patient had had none of the diseases of childhood. He has always been healthy with the exception of asthma, from which he has suffered severely for the last ten years. The history is negative as to pneumonia, pleurisy, malaria, rheumatism and nephritis. He has had gonorrhea several times, but denies syphilis. He drinks a great deal of whiskey and always has a drink before breakfast.

*Present Illness*: Started yesterday with a great deal of pain in the right chest, slight cough and great shortness of breath. The pain is worse today and the patient is unable to raise the mucus in his throat. He says he has been very blue in color for the past twenty-four hours. He was admitted to the hospital on account of cyanosis and dyspnea.

*Physical Examination*: The patient is fairly a well developed but poorly nourished man, showing marked cyanosis. There is orthopnea, apparently due to the dyspnea. His mental condition is extremely dull, he goes to sleep frequently while being examined and has to be aroused in order to obtain a history. He complains of being very tired and says he has had no sleep for two days.

The skin is very rough and dry and dark in color. The feet are extremely cyanotic; the hands are also cyanotic and show, on their dorsal surfaces, numerous dark brown, pigmented spots from one-half to one centimeter in diameter, resembling old syphilitic scars. The mucous membranes are cyanotic, moist, not pigmented.

The lymph glands show general enlargement.

The pupils are regular in outline; they are small and react sluggishly to light and accommodation.

There is marked pyorrhea. The pharynx is much congested. The veins of the neck are not distended. The thorax is barrel shaped, expansion poor.

Upon examination of the lungs the percussion note is high-pitched over the front and sides of the thorax and over the back as far down as the level of the sixth rib; below this on both sides the percussion note is of shorter duration and much less high-pitched. The breath sounds are almost inaudible except posteriorly below the level of the sixth rib. Many râles are heard throughout the chest.

The heart shows nothing remarkable except slight enlargement. The pulse is 120, regular, poorly sustained, easily compressible. The blood pressure of 90 millimeters of mercury.

The abdomen shows no tenderness or rigidity; there are no masses and no free fluid. The border of the liver is ten centimeters below the costal margin. The spleen is not palpable, but the area of dulness on percussion is increased.

All the reflexes are active.

The white blood corpuscles number 22,000.

On admission 15 minims of adrenalin were given; the blood pressure rose to 120 but fell again to 90 within an hour. The patient died from general collapse a few hours after admission.

At the autopsy, performed three hours after death, the findings were as follows:

Thrombosis of both adrenal veins, massive haemorrhagic infarction of both adrenals, organized thrombi in some of the small branches of the pulmonary artery, hyaline thrombi in some of the small meningeal vessels, acute bronchitis, pulmonary tuberculosis (active), tuberculosis of the liver (healed), tuberculosis of the spleen (healed), chronic pleuritis, pulmonary emphysema, arterio-sclerosis (aorta and coronaries), chronic interstitial nephritis (slight), chronic ulcerative colitis.

Both adrenals were somewhat large, and consisted of brownish-red friable masses, resembling old blood clot; on section a very thin layer of cortex, could still be made out, surrounding the brown homogeneous central portion. No suggestion of anything resembling tuberculosis in the tissues about the adrenals could be found.

*Microscopic*: Numerous sections from various regions of both glands were examined, and all showed practically the same picture. The changes in the left gland, however, were much less severe than those in the right. It was only with the greatest difficulty that one could make out that the tissue under examination was adrenal gland. The whole gland showed an extensive haemorrhagic infiltration, which was most marked in the medullary portion. The connective tissue stroma of the gland could still be distinguished, but the parenchymal cells were everywhere necrotic, appearing as pale pink staining debris, which in places still retained its typical arrangement in cords. In one or two small areas, a few parenchymal cells which retained their normal staining properties could still be made out. In some areas, especially about the borders of the gland, there were large numbers of polynuclear leucocytes, which for the most part lay imbedded in masses of fibrin. Many of these showed fragmentation of nuclei. They resembled closely the zone of leucocytes often seen at the margin of an infarct. The central vein was filled by an organized thrombus which showed in places canalization, the channels so formed being, in turn, filled with fresh thrombi composed of fibrin, with varying numbers of red blood cells and leucocytes. The larger branches were filled with similar fibrinous thrombi, while the smaller veins were filled with masses of coagulated cells, evidently of more recent date. In the capillaries numerous hyaline thrombi could be seen. No disease of the vessel wall could anywhere be made out. There was nowhere evidence of tuberculosis, and sections stained for tubercle bacilli, other bacteria and for *Treponema pallidum* all gave negative results. Sections through one of the neighboring sympathetic ganglia showed nothing abnormal.

There can be no doubt that in this case the haemorrhage was secondary to the thrombus formation in the veins. The thrombi in the central vein and in the larger branches were very definitely older than those in the smaller vessels. This could not occur if the haemorrhage were primary, for in such a case, as Simmonds has pointed out, the thrombus formation would take place first in the smaller vessels and the clotting in the larger vessels would follow later. Moreover, in cases where the haemorrhage is definitely primary, as in those produced by bacterial capillary emboli, thrombosis of the central vein is not found.

The pathological findings in this case are identical with the findings in the cases of infarction of the adrenals reported in the literature. Simmonds, Lissauer, Wooley, Lavenson, Arnaud, and Hektoen all describe the findings of thrombi of older date in the central veins and large branches, with more recent clots in the smaller vessels.

In searching the literature, one is at first struck with the apparent rareness of adrenal infarction, there being only some twenty or thirty cases reported. It must be remembered, however, that these cases are the observations of the very few who have had their attention called to the condition. When one considers that Simmonds of Hamburg had himself seen seven cases, while Lissauer at Breslau had met with four, one realizes that adrenal infarction cannot be so extremely rare, but that the great majority are probably overlooked.

That adrenal haemorrhage in the adult is much more common than is generally supposed is the opinion of all authorities. Thus Arnaud, who has written the classical description of this condition, found some degree of haemorrhage into the adrenals in one per cent. of his autopsies on adults. Such being the case, it is interesting to note that the only two observers who have studied massive adrenal haemorrhages from the point of view of infarction, have found thrombosis of the central vein present; the one in seven out of eleven cases, and the other in every one of the four cases studied by him. The adrenal haemorrhage occurring in the new-born is, on the other hand, not accompanied by venous thrombosis, but is in all probability due to trauma and the extreme congestion of the organs brought about during delivery by obstruction of the peripheral circulation.

From the above considerations it would seem that haemorrhagic infarction of the adrenals, while rare is deserving of greater attention than it has hitherto received, especially in the English and American literature, where, with the exception of three cases reported by Lavenson, Wooley and Hektoen, respectively, mention of the condition is almost wholly wanting.

The symptomatology of the condition appears to be identical with that of haemorrhage into the adrenals from any cause, and may be summed up in the single expression, "adrenal insufficiency." The two outstanding symptoms for which we must be on the watch are marked asthenia and a low blood pressure, pressures of 90, 80, or even 70 millimeters of mercury sometimes occurring. Bronzing of the skin and pigmentation of the mucous membranes, the essential signs of Addison's disease, are, as one would suspect, almost always lacking, the lesion being too acute for such a process to take place. The case reported here showed definite pigmentation, but the patient was extremely dirty and the pigmentation, I think, that of vagabondage rather than adrenal in origin. The diagnosis is undoubtedly difficult, but has been made on some occasions, and in the case here reported a lesion of the adrenal was suspected ante-mortem.

The etiology of thrombosis of the adrenal veins is very uncertain. Disease of the vessel wall has not been demonstrated in any of the cases and, in the opinion of most observers, plays no part in the process. Inflammatory lesions in the neighborhood of the organs have been found in some of the cases, as in the two of Arnaud's, in which there was, in one, a suppurating hydatid cyst of the liver and, in the other, an abscess of that organ, while

Lavenson's case showed an acute interlobular suppurative pancreatitis.

Simmonds considers the thrombi marantic, all his cases occurring in individuals suffering from a chronic illness—tuberculosis, malignant disease, myelitis, heart failure. This fact and the constant absence of disease of the organ, he considers sufficient ground for his opinion. He also calls attention to the anatomical arrangement of the vessels and thinks this favors the formation of marantic thrombi. Lissauer does not consider the thrombi marantic. He thinks that thrombosis occurs no more frequently in the adrenal veins than in other situations, but that the striking results of thrombosis of the adrenal veins call our attention to the lesion. It is interesting to note that in the case reported here there were, in addition to the thrombi in the adrenal veins, organized thrombi in the small branches of the pulmonary artery and hyaline thrombi in the meningeal and pulmonary capillaries. One of Lissauer's cases also showed organized thrombi in the small branches of the pulmonary artery.

The treatment of the condition narrows down to the giving of adrenalin or the feeding of adrenal gland. That any permanent good can be accomplished by such measures seems unlikely, as an organ necessary to life has been destroyed. However, in one-sided lesions, it is possible that an acute adrenal insufficiency might be tided over until compensatory production from the remaining portions of gland was established. The rise of blood-pressure following the injection of 15 minims of adrenalin was, in the case here reported, very striking, the pressure rising from 90 to 120 millimeters, only, of course, to fall rapidly again to 90.

## CONCLUSIONS

1. Haemorrhagic infarction of the adrenals occurs as the result of thrombosis of the adrenal veins.

2. The condition is more common than is generally supposed and is worthy of consideration as something more than a mere pathological curiosity.

3. Thrombosis of the adrenal vein is probably the commonest cause of extensive adrenal haemorrhage in the adult.

4. The diagnosis, while difficult, is possible and the condition should always be considered in patients with acute prostration with low blood pressure.

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5. The etiology of the thrombosis is unknown.

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# STUDIES IN THE BIOLOGY OF TUMOR CELLS.*

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## I. INTRODUCTION.

Tumors have been studied from many standpoints and yet there is little exact knowledge concerning the essential or basic conditions that determine their incidence, progress and proliferative capacities, or of the factors that govern the morphology, growth habits and capacity, and the arrangement and differentiation of their structural elements.

It is our purpose to discuss in the following pages the results of a study of certain aspects of the biology of tumor cells and to correlate them with certain recently established facts concerning the biology of cells in general, and especially those whose life histories are best known, namely, certain protozoa, sex cells, thymus cells, and certain functionally active metazoan cells, such as gland, ganglion and muscle cells.

These various kinds of cells possess many attributes in common. Protozoa, sex cells and tumor cells are capable under certain circumstances of unlimited growth, and both tumor cells and ova may survive the host from whom they spring and in whom they temporarily reside, and, further, each may live and grow within certain limits after transplantation.

R. Hertwig (1904) has compared tumor cells in their growth habits to a colony of protozoa, and another zoölogist, Moroff (1908), has pointed out certain close resemblances between protozoa and sex cells. The growth, multiplication and fate of protozoa and of sex cells may be modified experimentally in various ways, and, under these conditions, may exhibit certain variations in their physiology and morphology, as well as certain regulatory phenomena not always so evident in the normal state. As we shall show, tumor cells may and often do give evidence of the same attributes, and are governed in general by the same laws.

In order that the facts which we have established and the conclusions to be drawn therefrom may be clearly understood and correlated, it is necessary briefly to review the structure of protoplasm and nucleus, the relation of cell structure to function and certain other evidences of differentiation, depression, physiological degeneration and death of cells, the morphological and other changes in nucleus and cytoplasm in physiological degeneration and in recovery therefrom, the nucleus-plasma relation and its importance in cell life; and, finally the regulatory processes of protozoa, of sex cells, and of certain tissue cells.

## II. GENERAL CELLULAR BIOLOGY.

### THE STRUCTURE OF PROTOPLASM AND THE MODIFICATIONS PRODUCED BY FUNCTION.

The divergent views as to the structure of protoplasm which have from time to time predominated have been due, in large part, to the kind of cell used for study. The correctness of Bütschli's conception of the alveolar structure of protoplasm can no longer be doubted. The foam-like nature of cytoplasm is best seen in protozoan cells, but even here there are all gradations in the size of the alveoli, from the extremely minute ones met with in *Paramæcium,* for instance, alveoli so small as to give the protoplasm a finely granular appearance, to the coarsely meshed protoplasm of *Actinosphærium,* for example, in which the cytoplasm is sponge-like. In egg cells and in tumor cells the correctness of Bütschli's views can also be readily enough ascertained. In the case of metazoan cells it is in those with little or no functional differentiation that the alveolar structure is best marked. In protozoa it is the undifferentiated endoplasm which most clearly exhibits a typical "Schaumplasma."

As soon as an individual cell becomes functionally specialized and begins to take on activities peculiar to cells of its kind or species there occurs a more or less wide departure from the simple alveolar structure. Diversity of function leads to structural modifications and these give rise to the morphological differences which characterize the process known as differentiation. Depending upon the type of cell chosen for study, much evidence can be found to uphold the older ideas of the fibrillar structure of protoplasm of Remak, Max Schultze, Flemming, and others, and those of the net-like structure of Fromman and of Heitzmann. Even if one is unwilling to accept Altmann's bioblast theory in its entirety, one must admit that protoplasm may appear granular and that the granules present are, in some cases at least, living functional material, as has been amply shown in the case of enzyme secreting cells.

The fibrillar nature of the protoplasm of tumor cells has of recent years received strong confirmation by the work of Mallory, Thompson, Wolbach and others. The net-like structure is apparent in the intestinal cells of amphibia and other lower animals and in large ganglion cells.

Whenever, however, the simple alveolar structure of cytoplasm is departed from, the cell, whether metazoan or protozoan, is one of such unusual size as to require supporting fibrils or net-works, or of such highly specialized function that the departure from the alveolar structure must be considered the morphological evidence of the specialized physiological activity of the cell.

## NUCLEUS AND CYTOPLASM AND THE PART OF EACH IN CELLULAR ACTIVITY.

Just as the diversity of opinion as to the structure of the cell resulted from the type of cell studied and gave way finally to unanimity when the proper material was used by a mind able properly to value individual minutiæ and give them their place in a generalized whole, so also there have been various theories as to the chief seat of cell function. Again the diversity of opinion was dependent upon the type of cell selected for study. And, to carry the analogy between the two lines of cell study still further, again controversy is giving way to unanimity because of the study of the proper material.

In the earliest cell studies originated by Schleiden, Schwann, and their immediate followers the distinguishing morphological characteristic which made possible the identification of the individual cell as such was the delimiting membrane. To this was ascribed great functional importance.

With the development of knowledge and the recognition that protoplasm could undergo modifications, the cytoplasm became the all important portion of the cell, and the variations in the size, shape and structure of cells resulting from such modifications were looked upon as the morphological expression of cytoplasmic activity.

Investigations into the phenomena of maturation, division, and fertilization of sex cells brought to light the important rôle taken by the nucleus in a number of highly complex processes. The pendulum swung in the opposite direction—the nucleus became the essential element of the cell. Up to within very recent years the controversy has been maintained and much experimental work has been done to show, on the one hand, that denucleated portions of protoplasm might manifest the evidences of living matter and that non-nucleated cells might, theoretically at least, exist in nature; and, on the other hand, that nuclei might live after they had been freed of cytoplasm and that the latter was only of secondary importance in the life of the cell.

The earlier work of Maupas (1888, 1889) and of R. Hertwig (1889) upon the conjugation of the Infusoria, involving as it did at the same time the consideration of processes much like those which had led to the enthronement of the nucleus, and the study of cells able to manifest a great variety of activities other than those concerned in the so-called sexual process, was the beginning of a transitional period. Further work upon protozoa by R. Hertwig and his pupils led to the postulation by him (R. Hertwig, 1903 *a* and *b,* 1904) of a mutual interdependence of nucleus and cytoplasm. This doctrine of the nucleus-plasma relation has been the stimulus for a large amount of confirmative work, which enables one to state briefly that nucleus and cytoplasm are dependent upon each other for their existence and for the expression of their particular functions; that cellular differentiation, whether the cell be a free living or colony forming protozoön, or a metazoan sex or tissue cell, is the expression of this interdependence; that, of the various structures which help in producing morphological differentiation, certain ones are directly, others more indirectly, nuclear derivatives, and still others cytoplasmic derivatives formed probably under the influence of the nucleus; and, that, finally, differentiation is the means by which the single cell, whether it be free living or a member of a colony or tissue aggregate, exercises the highly specialized functions demanded of it as an individual.

## RICHARD HERTWIG'S NUCLEUS-PLASMA RELATION THEORY.

Based on Gerassimow's (1902) experiments upon the alga *Spirogyra,* and his own on protozoa and egg cells, R. Hertwig (1903*a,* 1903*b,* 1904) pointed out that for each cell there is an optimum size relation between nuclear mass and protoplasm mass which may not permanently be departed from in either direction without serious consequences, and in this connection he propounded his nucleus-plasma relation theory. According to this theory the nucleus-plasma relation of a cell is represented by the quotient obtained by dividing the nuclear mass by the protoplasm mass. This figure is constant for each kind of cell and, as long as it remains within certain physiological limits, the cell functions normally. If this is upset to the advantage of either nucleus or protoplasm the cell is abnormal, and before it can function normally it must restore its normal nucleus-plasma relation. Hence, there is a struggle between nucleus and plasma which tends to preserve a normal nucleus-plasma balance or equilibrium. R. Hertwig further explains cell division upon the basis of his nucleus-plasma relation theory as follows: In a recently divided cell the functional growth of the nucleus is relatively slow in comparison with that of the protoplasm, until, shortly before the next division, there occurs an upset in the nucleus-plasma relation to the advantage of the protoplasm, producing a nucleus-plasma tension which is the determining factor in division. At this critical point, there sets in a rapid growth of the nucleus—divisional growth—changing the nucleus-plasma relation in favor of the nucleus and ending in cell division, which results in a normal nucleus-plasma relation for the daughter cells. These observations and conclusions of Hertwig have been confirmed by Popoff's (1908) recent exact measurements of the volume relation between nucleus and protoplasm in *Frontonia.*

## CELL GROWTH.

Popoff's (1908) *Frontonia* work is of unusual importance because the conditions under which the cultures were kept could be held uniform from division to division. Since all cellular activities were, therefore, uniform from generation to generation one can leave out of consideration all functions except those concerned in cell growth. The variations within physiological limits of the relationship of nucleus and plasma could be accurately determined for every period in the life of the individual. This normal physiological variation is determined by the normal rate of growth of protoplasm for this particular cell.

### *Differences in the Rates of Cytoplasmic and Nuclear Growth in Frontonia at 25° C.*

When examples of *Frontonia* were kept at a uniform temperature of 25° C. and were daily given regular amounts of fresh water and food, division occurred every seventeen hours. The results of exact measurements made at regular intervals gave the growth curves given in Popoff's Figure 9 (Chart 1).

During the entire period, from one division to another, the bulk of the cytoplasm increases gradually with uniform regularity. The nucleus, however, shows, at first, slight decrease in size (which may be disregarded) and then a slower rate of growth than does the cytoplasm. This continues until the difference in the amount of growth reaches its greatest point during the fifteenth hour.

### *The Production of Nucleus-Plasma Tension and the Inauguration of Division.*

This point of maximum disproportion determines the moment of nucleus-plasma tension which inaugurates the divisional growth of the nucleus. During the sixteenth and seventeenth hours the nucleus grows rapidly, the increase in bulk being considerably greater during these two hours than during the entire previous fifteen hours. The disproportion in the relationship between plasma volume and nucleus volume, a disproportion which has been greatly in favor of the former, is overcome, and at the end of the seventeenth hour plasma and nucleus again bear the same relation to each other that they did at the beginning of the first hour. The volume of each, however, has been doubled and division occurs with the formation of two cells each with the volume of plasma and of nucleus, and with the relationship between the two, that are characteristic for *Frontonia* kept at 25° C.

By dividing the cytoplasm volume by the nucleus volume, obtained by measurements taken at regular periods, the nucleus-plasma relationship is mathematically expressed and plotted by Popoff in the curve given in Chart 2.

Leaving out of consideration the irregularity of the curve during the first four hours, due to the initial actual decrease in the size of the nucleus, the disproportion in the rate of cytoplasm growth as compared with that of nucleus growth is seen to be a gradually increasing one up to the end of the fifteenth hour, the moment of nucleus-plasma tension which inaugurates the rapid divisional

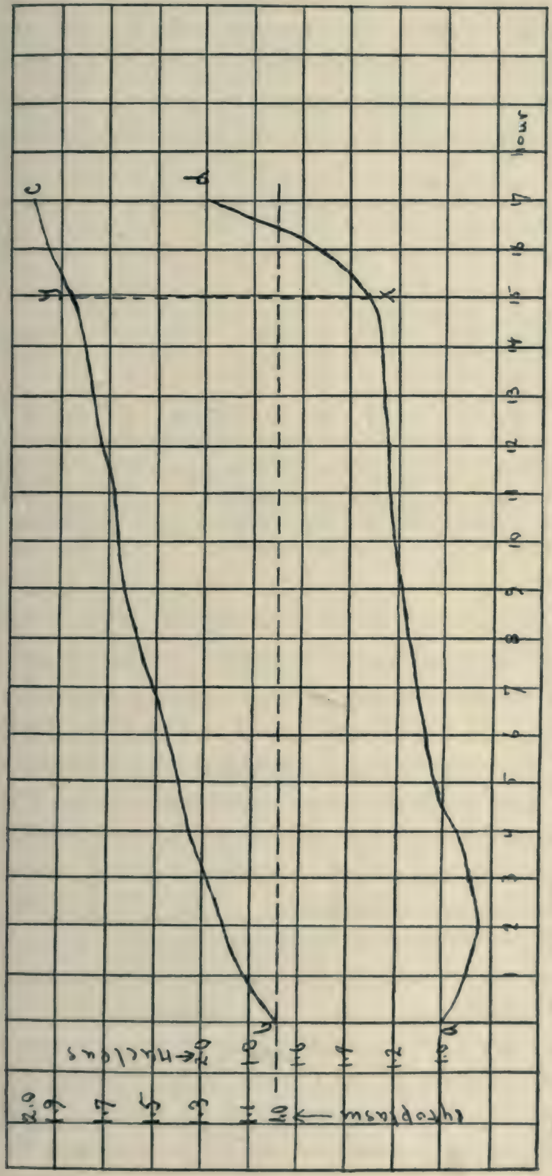


CHART I. (Popoff.) Growth curves of *Frontonia* at 25° C. *ad* represents curve of nuclear growth; *bc*, curve of cytoplasmic growth; *xy*, the point of maximum disproportion between nucleus and cytoplasm (nucleus-plasma tension); *xd*, divisional growth of nucleus; *ax*, functional growth of nucleus.

growth of the nucleus. At the end of the seventeenth hour, when division occurs, the relation between nucleus and plasma is again the same as at the beginning.

A uniform rate of cell growth is a property inherent in living protoplasm. But, because the greater rapidity of cytoplasm growth as compared with nucleus growth leads to an upset in the relation between nucleus and plasma, cell growth is sharply confined within definite bounds, the reaching of whose limits results in division.

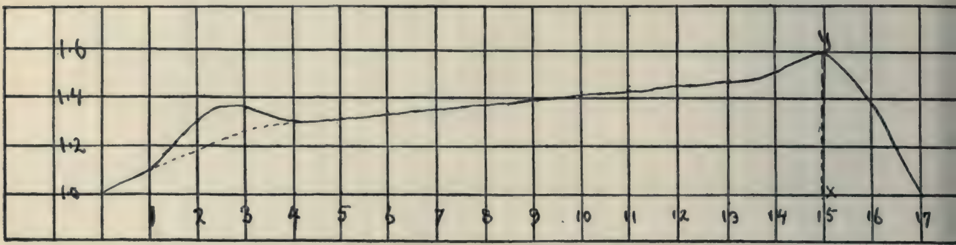


CHART 2. (Popoff.) Change in the nucleus-plasma relation, due to the variations in the rates of cytoplasmic and nuclear growth. *xy* represents the point of maximum disproportion between nucleus and cytoplasm (nucleus-plasma tension).

### *Alterations in the Growth Curve Due to Lowered Temperature:*

In *Frontonia* cultivated under uniform conditions at 14° C., nucleus and plasma show the same kind of growth curves, and the disproportion between the growth of the two is as gradually an increasing one as characterizes the organisms grown at 25° C. Cellular activities are, however, greatly reduced at the lower temperature and growth proceeds much more slowly. Division occurs every ninety hours instead of every seventeen hours. The slowing of the rate of nuclear growth involves not only the period of functional growth but also that of divisional growth. The latter becomes lengthened to over ten hours, instead of being able to complete itself in two hours as at 25° C. Cultivation in the cold leads to the formation of cells with a uniformly slightly greater size than is the case in those grown at 25° C. and with a permanently slower rate of growth. By the mere change in temperature, cell growth is so profoundly influenced as to increase the duration of the life of the individual over five hundred per cent. The important point, however, is that, although the size of the individual is permanently increased and the rate of nucleus and plasma growth permanently slowed, the volume relation between nucleus and plasma is the same at any given identical points when two or more generations are compared, and, furthermore, the curve runs the same course as in animals kept at 25° C. The nucleus-plasma relation of the animals cultivated in the cold has, however, become permanently changed, when compared with that for *Frontonia* grown at 25° C. This is due to the fact that the increase in nuclear bulk, due to cold, is greater than the increase in plasma volume. Although the nucleus-plasma relation curve has the same course in 14° C. animals as in those grown at 25° C., the curve runs at a different level. The changes which Popoff has noted in the growth curves of *Frontonia* grown in the cold—increase in the size of the cells, a permanent change in the disproportion between plasma bulk and nucleus bulk slightly in favor of the latter when compared with animals grown at 25° C., a permanent modification in the nucleus-plasma relation as compared with 25° C. cultures, slowing in the rate of cell growth and consequent prolongation of the time between divisions—all are the results of decreased cellular activities produced by the action of cold. And they are changes of the most profound importance when comparison is made between tumor cells and normal tissue cells.

Popoff appears to have proven experimentally the correctness of R. Hertwig's (1903*b*) contention that normal cell division is the result of normal cell growth and that the former is a regulatory process whose purpose is the control of the latter. The prime factor in division is the nucleus-plasma tension produced by the maximum disproportion between plasma and nucleus, a disproportion which is due to the greater rate of cytoplasm growth over that of nucleus growth. When the condition of nucleus-plasma tension has once inaugurated the divisional growth of the nucleus, division must occur and cannot be avoided. Cell growth and division automatically control each other.

## *Prolongation of the Period of Growth by the Prevention of Nucleus-Plasma Tension.*

That the factor of chief importance in division in its relation to normal cell growth is the condition of nucleus-plasma tension, which occurs at the time of greatest disproportion between nucleus growth and plasma growth, has been shown experimentally by Popoff in *Frontonia.* By removing a portion of the cytoplasm at a time before the divisional growth of the nucleus had begun, that is, at a time when the disproportion between nucleus and plasma had not yet reached its height, division of the cell could be delayed for varying periods. In one case, by repeating the operation from day to day as the removed cytoplasm was renewed by growth, but always at a period before the growth had reached such a maximum as to produce nucleus-plasma tension, division was delayed for a period of twelve and one-half days. The life of the individual was increased from ninety hours to three hundred and ninety hours —an increase of four hundred and thirty-three per cent., and this in a 14° C. animal, in which low temperature had already prolonged the growth period five hundred per cent. as compared with a normal 25° C. animal. Cell growth is, therefore, a property of normal protoplasm which can be almost indefinitely prolonged if conditions are so altered by slowing the rate of cytoplasm growth that the moment at which the preponderance of cytoplasm volume over nucleus starts the divisional growth of the nucleus is postponed.

## *Indefinite Prolongation of the Growth Period not Possible because of the Exhaustion of Growth Energy when Division is Prevented.*

Growth is not indefinite because the initial growth energy with which a cell is endowed is sooner or later used up even if nuclear division can be prevented. In Popoff's *Frontoniæ*, whose division was prevented by repeated operative removal of portions of cytoplasm, the cells finally went into physiological degeneration and died without division. The animals died with all the evidences of senility—sluggishness of motility, inability to take food and condensation of protoplasm. For the renewal of the energy used up in growth there become necessary certain phenomena other than the usual asexual division.

## UPSET OF THE NUCLEUS-PLASMA RELATION.

### *In Protozoa.*

It has been established by the work of Maupas, Calkins, R. Hertwig, and the latter's pupils, that certain protozoa, when cultivated for a considerable period of time, cease to multiply, go into depression and, finally, undergo physiological degeneration and die. Before complete degeneration and death take place, there occur alternate periods of depression and recovery with active multiplication. R. Hertwig (1900) discovered that during the depression periods the nuclear material is not only relatively but actually increased in relation to the protoplasm; that is, that the normal nucleus-plasma balance is upset in favor of the nucleus. In *Paramœcium, Frontonia* and *Stylonychia* in this condition larger and smaller portions of the macronucleus are broken off and destroyed. In *Actinosphærium eichhorni,* a multinucleated heliozoön, R. Hertwig (1904) has shown that in overfed cultures, there occur periods of rapid multiplication alternating with periods of deep depression. During the latter, there occur marked evidences of increase of nuclear material, as is shown by nuclear hypertrophy (and at certain stages producing giant nucleus formation), hyperplasia and hyperchromatism, associated with marked degenerative changes in the protoplasm, such as retraction, thickening and loss of pseudopodia, plasmogam, condensation and thickening of the protoplasm, and even areas of necrosis of the latter. The degenerative changes of the nuclei are pronounced and varied, and embrace dissolution and resorption of nuclei (the protoplasm of this animal has developed to a high degree the property of breaking down nuclear material), nuclear fusion, and, most remarkable of all, the reduction of nuclear material by the passage of chromidia from the nuclei into the protoplasm, where they are either broken down, often with pigment formation, or extruded. Thus by destruction of superabundant nuclear material accumulated during excessive function and rapidly repeated divisions, this animal may reorganize or regulate itself, and, so, recovering from depression, it may again feed and multiply. After depression and recovery have repeated themselves several times, the animals fall into fatal depression with hypernucleosis and markedly degenerated protoplasm—physiological degeneration—and the culture dies out. One of us (Howard, 1908) has confirmed and amplified Hertwig's findings in depressed *Atcinosphærium.*

### *In Sex Cells.*

R. Hertwig (1903 *a*), Goldschmidt and Popoff (1907), Popoff (1907 *a* and *b*) and Moroff (1909) have called attention to the occurrence of chromodiosis previous to division in sex cells. Popoff (1907*a*) has shown that after the rapidly repeated divisions of the spermatogonia and the ovogonia stages, the cells are in depression, make abortive attempts at division and finally regulate themselves by chromodiosis before division can start again. A large proportion fail to regulate themselves and die at this stage. It seems probable, indeed, that the maturation divisions of egg cells are in part, at least, regulatory phenomena. Sex cells after the maturation process are still in depression, for, unless conjugation occurs, they perish.

### *In Tissue Cells.*

It is a well-established fact that the cells of the blood have a relatively short life. The older leucocytes present various evidences of depression, including condensation and lobulation of their nuclei. Ganglion cells of old animals present striking evidences of an upset in the nucleus-plasma relation. Of the various somatic cells of which we have accurate studies, the thymus cells bear the most striking relation to our theme.

The development of the thymus and the life history of its cells have been studied recently in *Hypogeophis rostratus* by Marcus (1908). His findings may be epitomized as follows:

The cells of the thymus anlage are at first exactly like those of the neighboring intestinal epithelium from which it is derived—cylindrical epithelial cells with oval nuclei and a small nucleus-plasma relation. During a period of relatively slow growth the nuclei of the cells become larger, the cytoplasm decreases in amount, and the epithelium becomes lower, resulting in a nucleus-plasma relation somewhat in favor of the nucleus. The nuclei are now from 7.5 to 9.0 micra in diameter and the cell bodies are of considerable size. With the separation of the thymus vesicle from the intestine, there occurs an intensive growth, in which the cell divisions take place so rapidly that the daughter cells do not have the chance to reach the size of the mother cells. Thus the vesicle becomes a compact mass of small cells, the nuclei of which at the end of this stage have about half the surface of those at the outset. The cytoplasm is diminished even more in proportion, some cells possessing very little recognizable cytoplasm. In this manner arise the so-called "lymphoid" cells of the thymus, which are depressed cells with a nucleus-plasma relation markedly in favor of the nucleus. The nuclei have not only gained in size relatively, but are highly hyperchromatic.

While the chromosomes of the dividing nuclei in the previous stage are slender, delicate rods, now they are deformed, clumped in large, square or round ball-like masses, unfitted for exact division. This leads to pathological mitoses, and thus there occur all transitions from normal to degenerative nuclear and division structures—heteropolar mitoses, clumped chromosomes and single chromatic balls. At this time the organ is composed of a single type of cell, the "lymphoid" thymus cell, whose characteristics are indicated above. It can no longer divide and its functional and assimilation capacities must be at a low ebb: it must die unless reparation in some form occurs.

The next stage in the evolution of the organ is marked by the appearance of cells of the "epithelioid" type, originating from the "lymphoid" cells, which increase in size by growth of the cytoplasm. The nuclei of the "epithelioid" cells are hyperchromatic, increased to twice the normal size, and are diplocaryotic nuclei in Boveri's sense. When these cells attempt to divide, their chromosomes are ill-shaped and abnormally large, often to such a degree that division is arrested. From this abnormal state various reparative and degenerative changes may be traced. By reduction of the nuclei by chromidiosis and by growth of the cytoplasm there may be produced very large cells with pale nuclei. The most important degenerative changes are the production of achromatic nuclei, vacuolization and hyaline degeneration of the cytoplasm, and the degeneration of chromidia with the formation of larger and smaller masses of nucleolar substance, giving rise to eosinophilous granules in the cytoplasm. Further, in some nuclei there occur appearances strikingly suggestive of the synapsis stage of sex cells. Many of these large "epithelioid" cells fuse by processes (plasmogamy), as often observed in depressed protozoa, and form large protoplasmic masses with two or more nuclei. The central portions of such masses show various stages of degeneration and thus the Hassall bodies are formed.

Marcus sets forth the direct bearing of these various stages in the development of the thymus cell upon Hertwig's nucleus-plasma relation theory, and indicates the striking analogies between the depression states of the thymus cell and phenomena observed by Hertwig, Popoff, himself and others in protozoa and in sex cells. Marcus also indicates the relation of the changes in the thymus cell with metaplasias occurring in this organ—the development of mucous cells, striated muscle cells and ganglion cells—and with the various histological differentiations found in dermoid cysts.

## THE NUCLEOLAR SUBSTANCE.

In what has been said above, the ubiquitous relationship of the nucleus to the biological processes occurring in normal and abnormal cell life has been pointed out. In the diverse functions of the nucleus and in its varying relationships to the cytoplasm the acid staining material known variously as oxychromatin, nucleolar substance, plastin, pyrenin, etc., plays an important rôle. In what is to follow, the term karyosome will be used in preference to nucleolus and plasmosome. Whether the plastin present in the intranuclear body is combined or not with chromatin is a matter of secondary importance. The chief point is the presence in the karyosome of plastin.

### *The Relation of the Nucleolar Substance to Vegetative Function and to Reproduction.*

Moroff (1908), in his exhaustive study of several species of *Aggregata,* concludes that the karyosome has a purely vegetative function. Applying the doctrine of nuclear duality to nuclei which are morphologically single, he concludes that the karyosome is the somatic nucleus of the cell and is directly comparable to the macronucleus of the *Ciliata.* Up to a certain point one must agree with this author. The participation of plastin in the secretory activities of plant and animal cells is known. In these cells it may occur diffused throughout the nucleus, either combined or uncombined with chromatin, or it may be collected into a single larger intranuclear mass either free of chromatin as a true nucleolus or plasmosome or united with chromatin as an amphinucleolus or compound karyosome. But it is also a well-established fact that plastin takes part in the formation of chromosomes. Furthermore, the material of the karyosome plays an active part in the formation of those intranuclear, amitosis-like figures which are formed during the division of a number of protozoan nuclei, nuclei belonging to the type termed centronucleus by Boveri. The karyosome and its constituent nucleolar substance may have, therefore, not only vegetative or somatic functions, but also animal or reproductive properties.

### *The Rôle of the Nucleolar Substance in the Organization of Chromatin.*

The chemical differences between plastin and chromatin rest upon too insecure a basis to permit an attempt at the correlation of function and chemical composition. The recently expressed view of Růžička (1908), that plastin is a complex albuminoid or albuminoid-like substance built up from more labile protoplasmic compounds and that it may be broken down into the relatively less complex chromatin, is not at variance with known facts but adds nothing essentially fundamental for the explanation of those facts.

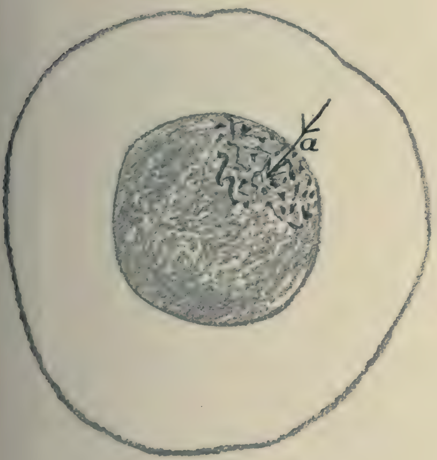
However varied or important may be the part taken by the nucleolar substance in nuclear and cellular phenomena, the chief virtue of the material lies in the relationship it bears to the chromatin. The most acceptable expression of this relationship we owe to R. Hertwig (1902*a*). Ignoring, in the present state of our knowledge of cytochemistry, the question of the nature of the nucleolar substance, Hertwig demonstrates the intimate relationship between this substance and chromatin, and explains the functions of the former by means of this relationship. According to him, the material from which chromatin is derived is formed in the cytoplasm and exists there in a form not to be recognized, because it has, at this stage, no characteristic staining reactions. The union, within the nucleus, of this prochromatin, if one may coin the word, with the nucleolar substance results in the formation of the basic staining material which we call chromatin, and in this organization the chromatin becomes visualized.

### *The Utilization and Fate of Chromatin in Cellular Function.*

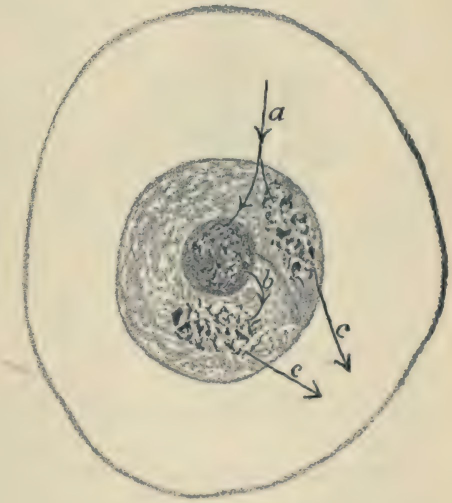
Excessive nucleolar substance may be stored in the karyosome, to be used in the further production of chromatin as may be required by the activities of the cell. From the nucleus, chromatin and its derivatives return to the cytoplasm to be used in the vegetative functions of the cell and in the formation of many of the morphological differentiations associated with these functions. When the chromatin leaves the nucleus in the form of granules or masses, the nuclear origin of these bodies is apparent from their property of being stained with the basic dyes. In the further changes which these chromidia may undergo, the basic staining property gradually becomes lost and the granule or mass takes the characteristic oxychromatin stain. An identical series of changes can be seen in the karyolysis and karyorrhexis which occur in a number of degenerative processes. As the basic staining material disappears from the nuclei the plastin again comes into view. Finally, this also loses its identity. It has been recently pointed out by one of us (Schultz, 1909, in association with Corlett) that in the production of keratohyalin in the epidermis there occurs a similar succession of changes.

Chromatin would seem to be, then, an unstainable material derived from the cytoplasm plus nucleolar substance. The latter is the material by which, on the one hand, the nucleus derives from the cytoplasm the substances necessary to the former and by means of which, on the other hand, the nucleus controls the varying activities of the cell. The nucleolar substance, therefore, is of prime importance in the interdependence which exists between nucleus and cytoplasm and is necessary for the maintenance of a proper nucleus-plasma relation.

Hertwig's idea concerning the nucleolar substance may be expressed diagramatically, and the same means may be used for amplifying this idea and for making clear certain of the events which occur in the regulatory phenomena necessary for maintaining the proper balance between the nucleus and plasma. In the diagrams the chromatin is represented by black, and nucleolar substance by shading.

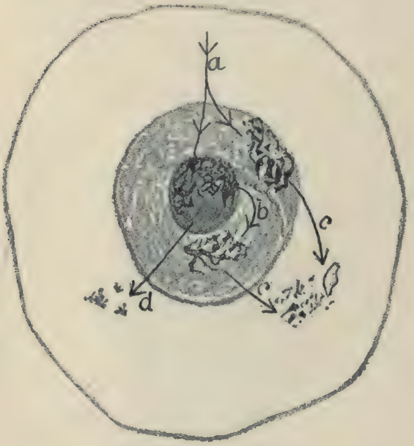


Text-figure 1.

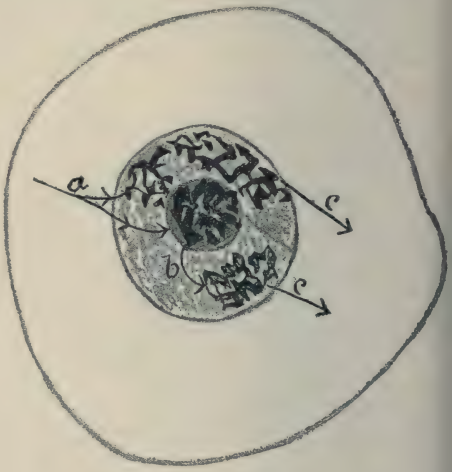


Text-figure 2.

The participation of the nucleolar substance in the formation of chromatin is illustrated by Text-figure 1, the passage of materials into the nucleus, where they become visualized as chromatin, being indicated in this and in Text-figures 2, 3, 4, 5, and 6 by the arrow (*a*). If there is no excess of nucleolar substance stored in a morphologically differentiated intranuclear body, this process results in the formation of a nucleus with chromatin more or less diffused. This chromatin visualization is only one side of the nucleus-plasma equation. In Text-figure 2 is shown a further stage, the passage of chromatin derivatives into the cytoplasm, there to be used in the activities of the cell. This step is designated by the arrow (*c*). If the nucleus contains a nucleolus, chromatin may be deposited here and then passed on in order to become diffused throughout the nucleus, as represented by the arrow (*b*). Text-figure 2 illustrates, in diagrammatic fashion, the course of events in the great majority of tissue cells, those cells with a not very active function. From the nucleus, materials are constantly given off to the cytoplasm as unstainable material, fresh chromatin is being constantly formed, and the two processes balance each other. Text-figure 3 represents the same series of events as Text-figure 2, except that cellular function is much more active, larger amounts of nuclear materials are necessary in the cytoplasm for the very active function, and there is a chromatin formation sufficiently active to keep nucleus and plasma in equilibrium. Such a process occurs in many protozoa and in certain metazoan cells, notably gland and ganglion cells. The increased demand of the cytoplasm for nuclear materials leads to the extrusion from the nucleus of masses and granules which take the chromatin stains, extranuclear chromatin of varied morphology making up the chromidial apparatus of Goldschmidt

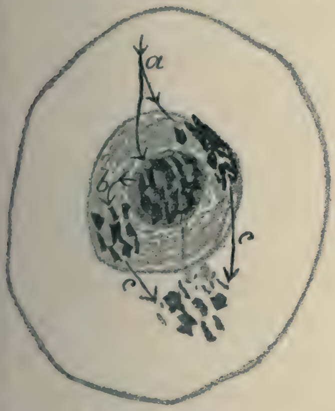


TEXT-FIGURE 3.

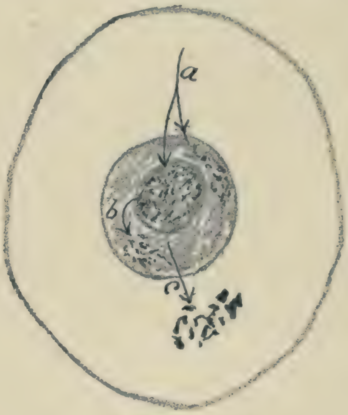


TEXT-FIGURE 4.

(1904*a*). Nucleolar substance uncombined with chromatin may also be given off to the cytoplasm, as indicated by the arrow (*d*). In Text-figures 2 and 3 we are dealing with cells with a normal nucleus-plasma relation because of the perfect balance maintained between the using up of nuclear materials (*c*) and the formation of chromatin (*a*). The remaining text-figures illustrate the mechanism in the disturbance of the nucleus-plasma relation due to abnormalites in one or both links of the chain. If in such a cell as is represented by Text-figure 2 the passage of nuclear materials into the cytoplasm (*c*) remains normal, or is decreased by loss of function, while the passage of chromatin forming materials into the nucleus is increased (*a*), the latter becomes loaded with chromatin, as shown in Text-figure 4. Such hyperchromatic nuclei are indicative of an upset of the nucleus-plasma relation in favor of the nucleus, a disturbance characteristic of the depression seen in protozoa, in certain stages of the development of sex cells, in thymus cells and in tumor cells. If now, as indicated in Text-figure 5, the passage of nuclear materials into the cytoplasm (*c*) can be increased to such a degree as to approximate almost or wholly the increased chromatin formation (*a*), the hyperchromatism decreases, the nucleus approaches the normal in appearance, and the depression is more or less completely overcome. One of the evidences of this increased passage of nuclear materials into the cytoplasm is the



TEXT-FIGURE 5.



TEXT-FIGURE 6.

presence of chromidia. Chromidiosis as a regulatory mechanism, a process for the reëstablishment of a normal nucleus-plasma relation, occurs in depressed protozoan, thymus and egg cells and, as we shall show, in tumor cells. In the production of depression characterized by hyperchromatism, actual or relative increase in chromatin formation is the active link in the chain of events. There is, however, the possibility of depression due to increased chromatin destruction, as shown in Text-figure 6. If a cell is thrown into a condition of functional hyperactivity the cytoplasm makes an increased demand upon the nucleus for nuclear materials. If the passage into the nucleus of those cytoplasmic substances which unite with nucleolar substance to form chromatin cannot keep pace with the excessive chromatin consumption, the chromatin originally present in the nucleus and in the karyosome disappears from both and the nucleus becomes pale. The cell is in a condition of depression because the nucleus-plasma relationship is markedly disturbed in favor of the cytoplasm. The end of the process is a complete dechromatinization of the nucleus and death of the cell. The occurrence of such a series of phenomena has recently been demonstrated by Dolley (1909) in hyperstimulated ganglion cells.

Whether, in this dependence of chromatin upon nucleolar substance, the necessary amounts of the latter are formed only in the nucleus from materials derived from the cytoplasm, or whether nucleolar substance can be preformed as such in the latter situation, cannot be definitely stated. The constant production of nucleolar substance, however, would seem to be a premise required for the explanation of the continuous formation of chromatin and the ceaseless transference of nuclear materials to the cytoplasm. That the production of nucleolar substance may become excessive and exceed all the probable demands of the cell we shall point out later in tumor cells.

## THE PREVENTION OF AND RECOVERY FROM DEPRESSION. REGULATORY PROCESSES.

### *The Avoidance of Depression.*

It has been pointed out in the foregoing pages that cells in general tend to fall into depression. In normal cells with a normal division rate, the functional activities of which are not interfered with, depression is avoided by the regularly repeated divisions and by the using up of nuclear and cytoplasmic materials in differentiation and functional activity. When, in cells readily capable of division, functional activity is increased, due to overfeeding in protozoa, for instance, there is marked increase of nuclear material and the nucleus-plasma relation is upset in favor of the nucleus. Division, as long as it can occur, tends to restore the nucleus-plasma balance. Calkins and Lieb (1902) have shown that the addition of certain salts to cultures of *Paramœcium* results in avoiding depression in this animal for many generations. Gland, muscle and ganglion cells find in functional activity a marked outlet for superabundant nuclear material. The extranuclear functioning nuclear material, which plays such an important rôle in these cells, called by various authors Nebenkerne, ergastoplasm, pseudochromosomes, mitochondria, chromidial net, etc., and correctly grouped together by Goldschmidt (1904*a*) under the term chromidial apparatus, is used up in cellular activities. This chromidial apparatus is of varied morphology, such as networks, fine and coarse fibrils, coils, and large and small round, oval and irregular masses. The secretion granules of pancreas and poison cells, the extranuclear chromatic substance of ganglion cells (the granules of Nissl) and of epithelial-muscle cells, all examples of chromidial apparatus, are used up in functional activity and renewed during rest.

### *Recovery from Depression.*

As cells may avoid depression by the use of certain regulatory processes, just so may they recover under favorable conditions from a depression otherwise fatal. Its nucleus-plasma relation once disturbed, the cell strives to restore it to the normal condition. The methods employed vary with the capacities and states of the cell. In cells fatigued short of exhaustion, the nucleus-plasma relation being in favor of the cytoplasm, the nuclear material is restored during a period of rest. This is well illustrated by the changes which occur in pancreas, ganglion and certain muscle cells.

When the nucleus-plasma relation in depressed cells is in favor of the nucleus, four methods of regulation are available: (1) cell division; (2) reduction of nuclear material; (3) increase of the cytoplasm; and (4) karyogamy.

Cell division, according to R. Hertwig's (1903*b*) conception is primarily a regulatory process by which the nucleus-plasma balance is restored, for it is preceded by increase in nuclear growth, results in reorganization of both nucleus and cytoplasm and leads to restoration of the normal nucleus-plasma relation. Very rapidly repeated divisions, however, as has been seen, result in cells with a nucleus-plasma relation markedly in favor of the nucleus, and divisions are arrested and may not be started again until, through some agency, the proper balance is restored.

Reduction of nuclear material is often brought about in depressed cells by nuclear fusion and resorption, extrusion of whole or parts of nuclei, and by chromidiosis, as has been shown by the work of R. Hertwig and his pupils. Chromidiosis, that is, the throwing out from nuclei into the cytoplasm, there to be broken down or extruded, of excessive chromatin staining nuclear material, was first described by R. Hertwig (1904) in depressed *Actinosphærium.* Since then, he and his pupils (Goldschmidt (1904 *a* and *b*), Popoff (1907 *a* and *b*), Marcus (1908), Kuschakewitsch (1907), and Howard (1908)) have shown that it is a widely adopted method in various protozoa, in sex cells and thymus cells of getting rid of excessive nuclear material and of restoring the nucleus-plasma relation. In most cases these last two processes, nuclear resorption and chromidiosis, are the chief dependence in preserving the integrity of the cell and in staving off physiological degeneration and death. As has been seen from the observations upon protozoa, sex cells and thymus cells cited in the foregoing pages, among multiplying cells, chromidiosis is commonly resorted to, and often enables cells to recover from depression and resume division.

The influence of growth of cytoplasm in restoring the nucleus-plasma relation balance is well illustrated by Gerassimow's experiments upon the alga *Spirogyra* and by Marcus's studies on thymus cells. The former (1902) found that when *Spirogyra* was submitted to cold, on division, one division product may contain no nucleus, and the other, two nuclei or one nucleus of double size. In the latter case the cell cannot divide until the cytoplasm has increased to a very great degree. Marcus (1908), it will be recalled, found that when after rapidly repeated divisions the cells of the thymus have fallen into marked depression, and the organ is composed of "lymphoid" cells, the cytoplasm of some of these cells grows markedly, thus forming the "epithelioid" cells, which may divide.

It has been shown by the studies of Calkins, R. Hertwig, and the latter's pupils, that the conjugation epidemics of certain protozoa occur during periods of marked depression, and if conjugation is prevented the animals finally die. Sex cells, though they preserve or regain divisional capacity through chromidiosis and other means, finally die unless fertilization ensues. In animals in which the type of conjugation is isogamous, as in *Actinosphærium eichhorni*, in deep depression even this opportunity for regulation and a fresh start may be debarred, for on account of the massive development of nuclear material the animal may not be able to encyst, or, if encystment is possible, the conjugation elements in the cysts may be so abnormal that the process is abortive.

R. Hertwig (1889, 1902*b* and 1903*b*) holds that conjugation is essentially a phenomenon of cell regulation without which the cell must finally perish. So far as is known, protozoa and sex cells are the only cells which have been able to preserve this most important regulatory process for the avoidance of and recovery from depression. In metazoa the soma perishes ultimately from physiological death; only the sex cells, which conjugate, have the capacity to live on indefinitely. In the nature of things, therefore, cells debarred from conjugation, although protected from the effects of accident, infection, toxemia, starvation, overwork and various harmful physical agents and the like, are destined ultimately to death from physiological degeneration. With the exception of prolonged overwork, the most distinctive mark and the apparent constant cause of physiological degeneration is excessive growth of nuclear material at the expense of the protoplasm.

## SUMMARY OF GENERAL CELLULAR BIOLOGY.

In the foregoing pages we have indicated and emphasized the main features in the structure of nucleus and cytoplasm and the known laws of cell growth, division and differentiation, and have shown, (1) that in order to prevent or postpone depression, physiological degeneration and death, cells must reorganize and regulate themselves; (2) that depression and physiological death in growing cells and tissue are associated with and dependent upon overgrowth of the nuclear material at the expense of the cytoplasm, that is, to an upset of the nucleus-plasma relation in favor of the nucleus; (3) that the change occurs especially in rapidly multiplying cells; (4) that the nucleus-plasma relation is intimately associated with cell division; and, finally, (5) that cells have developed several methods of regulation.

These regulatory processes are: (1) growth of cytoplasm, with differentiation, secretion and other methods of cell activity in which excessive nuclear material is used up; (2) cell division; (3) nuclear resorption and chromidiosis, often followed by cell division; (4) dissolution and extrusion of nuclei; (5) karyogamy.

## III. DESCRIPTION OF TUMORS.

### MATERIAL AND METHODS.

The material upon which this study of tumor cells is based has been collected over a period of several years from operations and autopsies. The operation material was fixed within a short time, often only a few minutes, after removal from the body, and for the most of it we are indebted to our colleagues, Professors Allen, Crile, Hamann and Robb.

As fixing agents, saturated aqueous sublimate solution, saturated aqueous sublimate solution and formalin, Flemming's solution and Zenker's fluid have been used. Surprisingly good fixation has been often obtained with formalin and with Orth's fluid. All material which did not show perfect fixation has been discarded. Great care has been taken to prevent shrinkage and other artefacts by the avoidance of rapid hydration and dehydration, and the use of graded alcohols has been scrupulously adhered to. Chloroform has been used for clearing and chloroform paraffin for embedding. As small, thin specimens have been used, the material has usually been kept in the paraffin incubator (50° to 55° C.) not longer than two hours. Only paraffin sections have been used, and the sections have been fixed to the slides by the water method and, therefore, never incubated.

As routine stains we have used Grenacher's alcoholic borax-carmin, either alone or followed by dilute Delafield's hematoxylin, Mayer's acid hemalum, Delafield's hematoxylin and aqueous eosin, and Heidenhain's iron hematoxylin, with and without eosin. As special stains, Mallory's fibril stains and the Biondi-Heidenhain triple stain have been resorted to.

## OUTLINE OF WORK.

The present work embraces a study of tumor cells as individuals as well as tissue forming cells. Therefore, it has been concerned especially with the study of the growth rate and other growth habits, and the differentiation capacity of tumor cells, the occurrence or non-occurrence of physiological degeneration among them and the regulatory processes by which the latter are avoided or recovered from. In short, the problem which we have set out to answer is, to what degree do tumor cells adopt and follow the same general biological laws which have been ascertained for protozoa, sex, thymus and certain other metazoan cells?

It is necessary to recall that different types of cells vary very widely in their capacity for division, the very highly differentiated cells like nerve cells, striated muscle cells and certain gland cells having either no divisional capacity, or a relatively slight one. In differentiation their idiochromatin has been completely or nearly completely lost, or perhaps on the same account their protoplasm has lost the power of performing its share in the division process. The various types of epithelium have very different capacities for division, germinal and covering epithelia having much greater power of division than that of glands, and certain glandular epithelia divide much more frequently and readily than others. Of the supporting tissues, fibrous tissues, vascular endothelium, glia, bone, cartilage and smooth muscle seem to respond to division incitants in the order named.

## CLASSIFICATION.

As growth is the most fundamentally important and universally applicable of the known attributes of tumor cells, our tumors are classified according to their rate of growth, as follows: (1) slow, (2) moderately rapid, and (3) rapid.

### *1. Tumors of Slow Growth.*

To avoid unnecessary details, descriptions of the well known structural characters of the ordinary benign tumors of fibrous, smooth muscle, cartilage, bone and epithelial tissues will be omitted. Speaking generally, these tumors are of slow growth and the differentiation of their cells is good and often perfect. Inter- and intracellular fibrils and ground substance are produced as in normal tissues. Careful study shows that in many such tumors, especially in the areas where the cell divisions have been more active, the cells are somewhat larger, both as regards cytoplasm and nuclei, than the cells from which the tumor has sprung; but there are, as a rule, few evidences of depression to be made out. Giant nuclei and giant cell formation rarely occur. The growth rate is so regular and slow and the differentiation capacities of the cells are so well preserved that the normal structure of the tissue is attained. When in such tumors the growth rate becomes accelerated, and differentiation is imperfect, evidences of depression are met with. Examples of this type are seen in fibromata and leiomyomata which become sarcomatous. In certain slowly growing fibrosarcomata, the bulk of the tissue is composed of cells rather than of fibrils, and many or even most of the cells are of the giant cell type, with a single nucleus, often in the process of budding. Here the divisions are more rapid, depression ensues, the cells do not form fibrils (fail to differentiate properly), and there may be a heavy mortality of the tumor cells from depression. A peculiar type of slowly growing sarcoma, with almost complete failure of differentiation, is illustrated by Tumor No. 1, a submucous tumor of the lower jaw of a boy of eight years.

*Tumor No. 1. Epulis of the Lower Jaw.*—The tumor, a small, ill-defined and unencapsulated growth, had been present for over two years before the excision of the portion submitted. Since it attained the size which attracted attention it has remained practically stationary. The clinical diagnosis was epulis, and at the first hurried microscopic examination the tumor seemed to be composed of large multinucleated giant cells lying in a nucleated, vascular stroma. Closer examination shows, however, that the ground substance is a protoplasmic mass containing rather large, oval, vesicular nuclei (Plate I, Fig. 1). The great vascularity is due, not to definite blood vessels, but to irregularly shaped, unlined blood spaces running throughout the syncytial tissue (Plate I, Fig. 2). The nuclei vary in size and show transverse diameters of 3.3 to 6.7 micra, and longitudinal diameters of 6.4 to 13.5 micra. They contain a rather wide-meshed reticulum upon which are deposited fine chromatin granules. Many nuclei show also two or several larger chromatin masses, and a considerable proportion are supplied with rather large karyosomes containing relatively little chromatin in the form of one or more granules.

The giant cells present bear a very definite relationship to the blood spaces and have been produced apparently in a mechanical way by the cutting off of multinucleated portions of protoplasm (Plate I, Fig. 3). The cell illustrated in this figure has a size of 58.1 by 37.1 micra. The giant cells thus produced do not appear to be capable of independent existence. They show all degrees of degeneration from irregularity of nuclear outline, condensation of chromatin and vacuolization of protoplasm (Plate I, Fig. 4) to nuclear fragmentation and destruction of the entire protoplasmic mass. In these degenerative changes the cytoplasm takes a faint, diffuse hematoxylin tinge. Individual, large mononucleated cells are also produced. These also seem to have been cut off mechanically by the blood spaces (Plate I, Fig. 2). Some lie free in the spaces. They are irregularly polygonal in shape, but do not take on the spindle form associated with advancing differentiation. They vary in length from 8.7 to 18.9 micra and even more, and in breadth from 3.7 to 8.7 micra. Their nuclei vary from 3.0 by 6.4 micra to 5.4 by 8.7 micra. In some of these cells the nuclei are hyperchromatic and irregular, and the cells seem to be in an early stage of degeneration. In very rare instances the protoplasm about a nucleus embedded in the syncytial mass stains in a slightly different tone and there is faintly outlined what appears to be the beginning of a cell—a process not due to the mechanical action of the blood spaces (Plate I, Fig. 2). From a few of the individualized cells fine fibrils extend. Nuclear figures are extremely rare—only two or three have been met with in a rather large number of sections studied. Histologically as well as clinically the tumor is one of very slow growth. It extends superficially to just beneath the mucosa of the gum, without invading the papillae and without having caused any flattening or atrophy of them.

The point of chief interest in this tumor is the extreme loss of the power of differentiation, a condition upon which is largely dependent the slow rate of growth. Because the formation of individual cells is interfered with and to a large extent prohibited, there is not attained such a relationship between nucleus and cytoplasm as permits a regular rate of cell multiplication. This tumor has also a very important bearing upon the origin of certain mixed tumors and syncytiomata and upon dermoid cysts, as will be indicated later.

The slowly growing malignant tumors of epithelial origin resemble in many respects benign tumors. In our experience, the slow growth depends upon (*a*) capacity of the cells to differentiate properly, (*b*) imperfect capacity of cell regulation and (*c*) slight divisional capacity, and (*d*) perhaps to the presence of the incitants to cell growth in only small amounts.

The tumors arising from stratified epithelia furnish numerous examples of this class. Arising from the layer of basal or germinative cells of the part which gives rise normally to cells which show a certain degree of morphological differentiation—fibril formation—and produce pigment, but are otherwise devoid of secretory activity and which have a considerable degree of division capacity, these tumors show great variation in growth rate and in differentiation capacity.

The common type of epithelioma of slow growth resembles an inverted skin papilloma and shows a reproduction of true differentiated epidermis with the various layers of morphologically differentiated cells with fibril formation, the central cells undergoing keratinization. The divisions here are not numerous at any one time and occur always in the peripheral or basal cells. The older cells are pushed towards the centre of the alveoli. Such tumors rarely form metastases and do not invade deeply. The division factors are inactive, the cells divide slowly and differentiate very much as in normal skin. The nucleus-plasma relation is disturbed to the advantage of the nucleus in many of the cells.

The so-called basal cell epitheliomata grow slowly, show but few division figures and form long thin or thick masses of cells with relatively very large hyperchromatic nuclei and a very small amount of cytoplasm. They differentiate but poorly morphologically, either in size or fibril formation, and, with their relatively large hyperchromatic nuclei, bear all the marks of depressed cells. They represent tumor cells acting under mild division incitants and not having the capacity efficiently to use either ordinary or acquired methods of regulation.

A third group of slowly growing epitheliomata springing from stratified epithelia is characterized by closely packed alveoli of the carcinomatous type and entire absence of differentiation. There is no attempt at the formation of epidermis and no difference between the characters of the cells at the margins and those in the center of the alveoli. Contrary to what obtains in the first group above described, cell division is not limited to the cells of the external layers, but may occur in any of the cells of the alveoli. Keratinization and "pearl" formation are absent. The majority of the cells are in marked depression, as shown by hypertrophy (often giant nucleus formation), hyperchromatism and various degenerations of the nuclei. Giant cells with a single large or with many small nuclei are numerous. The mortality of cells from irrecoverable depression is a marked feature of these tumors. Nuclear budding, the importance of which as a regulatory process will be developed later, is the only discernible evidence of regulation. In these tumors the incitant to cell division is evidently strong, but increase in bulk of tumor tissue is slow, because, on account of failure to develop satisfactory regulatory processes, a large proportion of the cells fall into hopeless depression and finally die. For the same reason metastases do not occur. Tumor No. 2 well illustrates this group.

*Tumor No. 2. Epithelioma of the Mucosa of the Right Cheek.*—The patient, a man of 60 years, was admitted to the service of Dr. G. W. Crile, September 2, 1907. Some months before, he had noticed three small papillomatous growths of the mucosa of the right cheek, at a point where the membrane was irritated by a broken tooth. The growths and the tooth were removed. On admission, on the inner aspect of the right cheek there was a small hard growth with an ulcerated, crater-like center. The tumor was removed at operation.

The growth consists of larger and smaller alveoli of oval and polygonal epithelial cells supported by a well-marked and vascular connective tissue stroma. The alveoli are not of uniform size and are usually elongated. The cells within the alveoli vary in size, but show no evidence of differentiation. The marginal and the central cells show no distinctive differences, and there is no keratinization and no formation of "pearls."

The type cell of the tumor, as found in the growing areas among cells showing mitoses, measures 17.0 by 15.0 micra, is round, oval or polygonal, with a finely alveolar cytoplasm and a rather large round or oval vesicular nucleus, whose meshwork is quite wide. The nucleus contains one fairly large, deeply staining karyosome, and numerous small chromatin granules scattered over the reticulum. The sections include the whole depth of the growth. In the more superficial portion, the alveoli and the tumor cells are much larger than in the deeper portion. In the latter, which is evidently the younger growing portion, there are fairly numerous mitoses. They are bipolar, but very rich in chromatic material. Even in this portion of the growth, the cells vary very much in size. In the older portion, there are few or no mitoses. Nearly all the cells are large, with large single hyperchromatic nuclei, or multiple nuclei, the result of budding. Types of these large or giant cells measure as follows: 21.5 by 16.0, 30.0 by 16.0, 38.0 by 25.0, 51.0 by 23.5, and 61.5 by 28.0 micra. (Plate I, Figs. 5 and 6, Plate II, Figs. 7, 8 and 10.) All gradations of nuclear hypertrophy and hyperchromatism can be traced up to large giant nuclei containing numerous large and small round and oval chromatic masses (Plate II, Fig. 8). The giant hyperchromatic nuclei may undergo direct division with the formation of two nuclei of equal size, budding with the formation of one or more daughter nuclei (Plate I, Fig. 6, Plate II, Fig. 7) or various forms of nuclear degeneration. The chromatic material may become diffused and present a homogeneous mass, with or without vacuolization (Plate II, Fig. 9), or break up into a large number of small round or oval masses which may become vacuolated (Plate II, Fig. 10). In such depressed cells vacuolization and hyaline degeneration of the cytoplasm are frequent and the cells perish. There is no evidence of chromidiosis.

Tumors similar to the above are found in the skin and the cervix uteri.

The slow growth of tumors springing from glandular epithelium, especially in the pancreas, is often due to the marked depression and lack of regulatory processes of their cells.

Many slowly growing malignant tumors, especially of the skin, are, doubtless, kept going, when otherwise they would stand still or even die out, by renewed beginnings of growth from new foci in the neighboring original tissue—pluricentric origin.

### 2. *Tumors of Moderately Rapid Growth.*

To this class belong (1) tumors that grow slowly at the start but that, through the development of regulatory processes and, perhaps, through an increase in the incitants to division, take on more rapid growth, and (2) tumors that grow moderately rapidly from the beginning.

In the first division belong certain sarcomata starting as fibrosarcomata, and carcinomata arising from slowly growing epitheliomata, which have developed nuclear reduction by amitosis, budding and chromidiosis; and certain sarcomata starting from fibromata and leiomyomata and certain carcinomata springing from benign epithelial tumors, in which the growth acceleration is best explained by assuming the accession of an increase in the growth incitants. The future history of such tumors is governed by the degree of regulation that they can accomplish.

In the second division, composed of tumors whose growth rate is moderately rapid from the start, certain types of regulation are, in our experience, always present. In a certain group of these, notably the adenocarcinomata of the intestines and uterus, the tumor cells do not fall into marked depression, probably because, as is suggested by the morphology of the individual cells, there is retained a degree of differentiation compatible with a considerable amount of functional activity—mucous secretion, etc. In these growths it is evidently only the increased divisional activity that distinguishes them from benign adenomata. We have, however, occasionally met with adenocarcinomata of the intestine in which many of the tumor cells were in fatal depression. In another group, in which many cells fall into marked depression and many die, the most marked regulatory processes are amitosis and nuclear budding. The latter is often followed by both direct and indirect division. Chromidiosis and nuclear resorption are comparatively rare, but when they occur, a higher degree of regulation and less well marked depression are met with.

*Tumor No. 3. Metastasizing Giant Cell Sarcoma of the Esophagus.*—Of the tumors giving clinical and microscopic evidence of moderately rapid growth, the first to be detailed is a metastasizing giant cell sarcoma of the esophagus, which shows certain interesting phenomena associated with amitotic division and nuclear budding.

The patient had exhibited clinical symptoms referable to the tumor for about one year previous to death.

At autopsy, the esophagus showed a large fungating tumor mass, most prominent at a point opposite the tracheal bifurcation and extending from here to the lower end of the esophagus. The tumor showed numerous areas of necrosis and of hemorrhage. The bronchial lymph glands were involved and the majority were necrotic. Numerous nodules of a pinkish gray color were present in the liver. Both adrenals were enlarged by the presence of tumor metastases, situated chiefly in the cortical portions of the organs. In the adrenals the tumor tissue contained small areas of brownish pigment.

The tumor is composed of closely packed cells of varying size and shape, showing no tendency toward alveolar arrangement. There is a very slight amount of intercellular connective tissue stroma. Wide, thin-walled blood vessels are numerous.

In the older portions of the tumor the cells vary in size from those measuring

10.1 by 14.5 micra to giant cells even larger than the one shown in Fig. 12 (Plate II). The latter measures 52.0 by 58.1 micra. In the smaller cells the nucleus has average measurements of 7.7 by 9.1 micra. It has a rather coarsely meshed reticulum and a definite membrane. Upon the former and upon the inner surface of the latter are deposited fine chromatin granules. In the nuclei of cells of medium size there occur, as well, larger round chromatin masses (Plate II, Fig. 11). The nucleus of a cell of the smaller size contains a single karyosome, usually loaded with chromatin and of an average diameter of 2.0 micra. Occasionally the nucleus may contain two karyosomes and, under conditions to be pointed out later, even more than two. The majority of these nuclei are vesicular and appear well regulated. Hyperchromatism occurs in the smaller cells, but is never very marked. Mitoses are very numerous.

In the larger cells the cytoplasm is more coarsely meshed than in the smaller ones and the nuclei are often hyperchromatic and lobulated. Mitoses among these larger cells are numerous, but in many the nuclear figure is disrupted and the chromosomes are in part fused with each other and in part widely separated throughout the cell. Almost all the larger cells show evidences of nuclear budding, but only rarely does one see a cell with even the slightest amount of extranuclear chromatin. Cells with budding nuclei are well supplied with cytoplasm—the large size of the cell is not due entirely to nuclear hypertrophy. Many of the exceptionally large giant cells are invaded by polymorphonuclear leukocytes.

That the nuclear budding so frequently seen in tumor cells is a purposeful process whose aim is a decrease in hyperchromatism is shown in Plate II, Figs. 12 and 13, and Plate III, Figs. 14 and 15. Giant nuclei which show no evidence of budding may be so loaded with chromatin that no finer structure is visible. With the beginning of budding the nucleus and its buds stain less deeply (Plate II, Fig. 12), and the greater the degree of budding, the more vesicular do the buds and the mother nucleus become (Plate II, Fig. 13, and Plate III, Fig. 14). The process leads to a marked increase in the surface area of the nucleus. If, at the same time, the amount of chromatin is not increased, the hyperchromatism must be decreased or overcome. The process leads finally to the formation of mutiple nuclei of the primitive vesicular type met with in the advancing margins of the tumor. In giant cells with multiple nuclei of this type, degeneration of individual nuclei may occur (Plate III, Fig. 15). Such an end phenomenon in the process of nuclear budding leads not only to a decrease in the amount of chromatin in the individual daughter nuclei, but also to an actual decrease in the amount of chromatin present in the cell.

At the advancing margins of the tumor, the cells are small, 11.4 by 14.1 micra, and have nuclei measuring 7.4 by 8.7 micra. The nuclei are vesicular and have a coarse reticulum upon which is deposited a small amount of finely granular chromatin (Plate III, Fig. 16). Each nucleus possesses one, very often two, and sometimes several karyosomes. In their structure and in certain phenomena relating to the karyosome these nuclei bear a striking resemblance to certain primitive protozoan nuclei, as will be pointed out later. At this point we wish merely to indicate the occurrence of changes in which the karyosome plays a part.

In a small number of cells the nucleus contains a chromatin-free, plastin karyosome (Plate III, Fig. 17). Various stages of chromatin deposition within the karyosome can be seen, until finally the nucleolar substance becomes almost entirely hidden by chromatin (Plate III, Figs. 16 and 18). The average diameter of such chromatin-laden karyosomes is 2.0 micra. The relationship of the karyosome to chromatin production may become abnormal in two directions. Some nuclei show hypertrophied chromatin-free karyosomes, which may be vacuolated (Plate III, Fig. 19). Others contain several hypertrophied plastin nucleoli (Plate III, Fig. 20). In such cells the cytoplasm is usually vacuolated. Abnormality in the opposite direction is met with when the hypertrophy of the karyosome is associated with chromatin formation. Such a process leads to the production of large, intensely stained intranuclear bodies (Plate III, Fig. 21). Continuation of the process leads to a diffusion throughout the nucleus of chromatin in the form of fine granules (Plate III, Fig. 22) and finally to a condition of hyperchromatism so extreme that the nucleus becomes transformed into an almost solid mass of chromatin (Plate III, Fig. 23). These evidences of progressive hyperchromatism are associated with gradual increase in the size of the affected cell.

A striking thing in these cells of the advancing portions of the tumor is the presence in many of the nuclei of two or several chromatin-containing karyosomes of equal or unequal size. At first glance such a condition seems to be purely fortuitous. Closer study shows, however, that these nuclei can be grouped in definite series. There occur karyosomes which show binary equal division of the contained chromatin mass (Plate III, Fig. 24). Still others are elongated and dumb-bell shaped, the two knob-like ends being united by a distinct band (Plate III, Figs. 25 and 26). The ends draw apart from each other, but even after the separation has proceeded to a considerable degree the daughter karyosomes may remain united by fine strands (Plate III, Fig. 27). There occur, finally, complete separation of the two karyosomes and gradually increasing indentation of the nuclear membrane (Plate III, Figs. 28 and 29). The end result is the production of two nuclei of equal size, each with a central, chromatin-containing karyosome (Plate IV, Fig. 30).

The process becomes slightly modified when the binary division of the karyosome is not an equal one. One sees nuclei with a larger and smaller body united to each other with fine strands (Plate IV, Fig. 31), other nuclei with two unequal karyosomes widely separated (Plate IV, Fig. 32), and finally a larger nucleus with a smaller bud (Plate IV, Fig. 33).

Still another modification of the process is characterized by multiple division of the karyosome, the daughter products remaining united by fine strands for some time (Plate IV, Fig. 34). After separation of the daughter karyosomes (Plate IV, Fig. 35) the nuclear membrane becomes indented in several places (Plate IV, Fig. 36) and there are formed as many buds as there are karyosomes present.

In the advancing portions of the tumor those cells whose nuclei are undergoing the processes of binary fission and of single budding outlined above are well regulated and have a fair amount of cytoplasm as compared with the nuclear volume. Those cells whose nuclei show multiple budding are all of larger size than the type cells. Cells with hypertrophied plastin karyosomes are also above the average size.

In this tumor differentiation does not occur, and there is no chromidiosis. Depression, toward which there is a marked tendency, is overcome by nuclear budding, and regulation is accomplished by mitosis and direct division.

*Tumor No. 4. Epithelioma of the Cervix Uteri.*—The growth involved a considerable part of the vaginal portion of the cervix uteri.

Material for examination was excised on two occasions; the first, four months after the first clinical symptoms appeared, and the second, three months later. The material obtained at both operations consists of numerous elongated or oval alveoli containing from one to four or five rows of rather flat, round or polygonal cells of the epithelial type. The interstitial tissue is comparatively scanty. Differentiation is poor. Keratinization and "pearls" are absent. Unlike what obtains in the more slowly growing epidermoid carcinomata with considerable differentiation, there are no distinctive marks between the size and appearances of the cells at the margins of the alveoli (basal cells) and those internal to these, and mitotic division occurs indiscriminately among the cells of the various rows in the alveoli. There are no appearances suggestive of attempts to reproduce tissue of the epidermal type so commoly seen in epidermoid carcinomata.

The type cell (Plate IV, Fig. 37) of this growth measures 17.0 by 13.8 micra and has a round or oval, rather vesicular nucleus, and finely reticular, faintly eosin staining cytoplasm. In these cells the nuclear chromatin is often in finely divided masses and granules scattered over the widely meshed reticulum. The majority of the cells are well regulated and evidently capable of active proliferation. Examples of depression, cytoplasmic and nuclear degeneration and necrosis, are, however, fairly numerous both in large giant cells and in small cells.

Nuclear hypertrophy with marked hyperchromatism and considerable growth of the cytoplasm are frequently met with. Many such nuclei (Plate IV, Fig. 38) show large central karyosomes, with numerous smaller chromatin staining masses scattered on the nodes of the nuclear meshwork. These nuclei may make abortive attempts at mitotic division, which may end in degeneration of the chromosomes in the spireme stage (Plate IV, Fig. 39), or they may divide by amitosis (Plate IV, Fig. 40) or by nuclear budding (Plate IV, Figs. 41 and 42). In nuclei which undergo multiple budding, the chromatic material does not continue to increase, for the nuclei produced by budding are always less hyperchromatic than the original mother nucleus from which they spring. The number of giant cells is considerable. Some have a single giant nucleus, but in most there are multiple nuclei, as many as twenty being not uncommon, the result of active budding from the mother nucleus (Plate IV, Figs. 42 and 43). The cytoplasm of these giant cells may be normal (Plate IV, Figs. 41 and 42) or vacuolated (Plate IV, Fig. 43). There occur both mononuclear and multinuclear giant cells in further stages of degeneration. Fig. 44 (Plate IV) shows a giant cell with two nuclei. One-half of the cell is dead, the cytoplasm completely hyalin and its hyperchromatic nucleus is in advanced vacuolar degeneration. The other end of the cell shows vacuolar degeneration of both cytoplasm and hyperchromatic nucleus. More or less complete hyalin degeneration with death of the cell and karyorrhexis with the dispersion of nuclear fragments throughout the hyalin cytoplasm are not of infrequent occurrence (Plate V, Fig. 45). Fig. 46 (Plate V) represents a huge giant cell, 74.5 by 345.0 micra, whose original nucleus, after sending off numerous buds, has undergone marked degeneration and is disintegrating. Most of the cytoplasm is hyalin and dead. The three pale staining areas containing nuclear buds are still unchanged. There is evidence that such nucleated areas may separate off from the mother cell and from independent cells.

Besides the giant cells there are many small cells, often smaller than the type cell, which are in depression, with relatively large hyperchromatic nuclei and a small amount of hyalin cytoplasm (Plate V, Fig. 47). Altogether the mortality of cells from depression is considerable in this comparatively well regulated tumor.

In other tumors (Tumors Nos. 2 and 3) it has been made apparent that nuclear budding represents a partially successful effort at nuclear reduction in cells whose nuclear material is too great to be divided by the ordinary division methods. Certain cells of this tumor offer evidence even more striking of the active purposeful nature of the budding process. Fig. 48 (Plate V) shows a cell containing three nuclear buds and a part of a mitotic figure in cross section; in Fig. 49 (Plate V) another cell with a cross section of a mitotic figure shows at one side a large number of degenerated nuclear buds. Fig. 50 (Plate V) shows a cell in the early anaphase of mitotic division with a mass of fused degenerated nuclear buds being cast from one pole of the cell. It is evident that in these cells the original nucleus has so decreased its bulk and its hyperchromatism by budding divisions that it has been able to accomplish mitosis, and that the cytoplasm is able to rid itself of this excessive nuclear material by extrusion. This hitherto undescribed regulatory process plays an important rôle in this tumor.

As usually obtains in the epidermal carcinomata, the cells of this tumor do not form chromidia.

*Tumor No. 5. Hypernephroma of the Adrenal of a Steer.*—A tumor of the adrenal of a steer is placed among the tumors of moderately rapid growth, although we have no knowledge of the clinical duration of the neoplasm. The tumor, a large mass, had entirely replaced an adrenal, without invading the kidney or surrounding structures. The tumor mass extended along the lumen of the adrenal vein and into the lumen of the inferior cava for a considerable distance. It was nowhere attached to the wall of the cava, and the endothelium of the latter was everywhere normal.

Histologically the neoplasm is a typical hypernephroma. It is composed of irregularly spheroidal cells lying in a reticulum formed by compressed capillaries. Most of the nuclei are round and vesicular. We believe that the tumor was one of moderately rapid growth because of its size and of the well regulated condition of the majority of its cells. Absence of invasion of surrounding tissues and the absence of metastases further indicate that the rate of growth was not very rapid.

In this tumor regulation occurs chiefly by the extrusion of chromatin. In this it is an exception to the rule that tumors of moderately rapid growth do not form chromidia. The reason for this lies in the fact that the tumor is derived from cells which normally have the property of transforming chromatin into pigment, and it is to illustrate this process that the tumor is included here. Certain cells with somewhat hyperchromatic nuclei show both extranuclear chromatin and granules of brown pigment (Plate V, Fig. 51). In other cells the nucleus stains more faintly and the amount of pigment in the cytoplasm is increased (Plate V, Figs. 52 and 53). Finally, cells in which no nuclei can be seen, but which are loaded with pigment are not unusual (Plate V, Fig. 54). The pigment occurs in the form of fine granules and larger round and oval masses. In the pigmented cells increase of pigmentation and decrease in the amount of nuclear chromatin go hand in hand.

### *3. Tumors of Rapid Growth.*

In this division, as in the second, two groups are to be distinguished: (1) tumors which, starting with slow or moderately rapid growth, develop rapid growth, and (2) tumors whose growth is rapid *ab initio.*

We have met with a number of examples of the first group. Invariably many or even most of the cells in the older parts of the growth are in depression and incapable of mitosis. Often there is a high percentage of death from physiological degeneration among the cells in these areas. A variable proportion of the cells show one or more regulatory processes, direct division, budding and chromidiosis. In the rapidly growing areas of such tumors the picture is reversed; comparatively few cells are in depression, and most of the cells are well regulated. The most conspicuous regulatory processes in evidence here are chromidiosis and nuclear resorption.

Examples of this group are furnished by carcinomata springing from slowly growing epitheliomata of the skin and tongue which, after moderately rapid growth, suddenly grow rapidly and metastasize freely in the tissues and lymph glands of the region. In these, however, chromidiosis has not been observed, and amitosis and nuclear budding are the chief regulatory processes. In numerous sarcomata and in certain carcinomata of glandular organs, chromidiosis (sometimes with pigment formation) and nuclear resorption, as well as amitosis and nuclear budding, are prominent regulatory mechanisms. Tumors Nos. 6 and 7 illustrate these points.

*Tumor No. 6. A Recurring, Metastasizing Carcinoma of the Thyroid.*—A male patient, aged 38 years, was admitted to the Lakeside Hospital, service of Dr. Dudley P. Allen, with a tumor of the neck which had been first noticed twenty years previously as a small mass in the left thyroid region. There had been no symptoms of exophthalmic goiter. At the time of the first operation, November 10, 1905, a tumor mass measuring 33.0 by 22.0 by 15.0 cm., situated in the region of the left lobe of the thyroid, was readily shelled out. In June, 1906, another mass was noticed in the position of the original tumor. This grew rapidly and was removed on December 11, 1906. It was easily removed except at the base, where removal was not complete. Recurrence was noticed soon after leaving the hospital. The tumor grew rapidly, and in July, 1907, made its appearance on the right side of the neck. Growth was rapid until readmission to the hospital on November 21, 1907, shortly after which the patient died.

At autopsy the entire anterior neck region was occupied by a large, lobulated tumor mass of a dark red color. The cervical lymph glands were markedly enlarged. The tumor showed many large areas of necrosis. In the lungs were numerous metastases varying in size from two to thirty millimeters.

Material removed at the first operation shows a tumor composed of alveoli varying in size and separated from each other by a small amount of vascular stroma. The alveoli are composed of closely packed cells which have a small amount of granular cytoplasm and whose nuclei have diameters of 5.4 to 6.7 micra. Such nuclei are vesicular, with a closely meshed reticulum upon which is deposited finely granular chromatin. A fair proportion of nuclei reach a diameter of 9.1 micra, and very hyperchromatic giant nuclei measuring as much as 15.2 by 20.2 micra are not infrequent. In the latter there are no evidences of budding. In the cells of medium size some finely granular extranuclear chromatin is seen, but chromidiosis is not very active. Mitoses are not numerous.

In the recurrence removed on December 11, 1906, the alveoli are, in general, smaller than in the primary tumor and there is less interalveolar stroma. The alveoli have no lumina. There is greater variation in the size of the nuclei, many having a diameter of only 3.0 micra. Giant nuclei are present, but do not reach so large a size and are not so numerous as in the primary tumor. Hyperchromatism, particularly of small and medium sized nuclei, is more marked. Little extranuclear chromatin is seen. Mitoses are present in small numbers.

In the local tumor removed at autopsy the general architecture is the same as above, except that at the peripheral portions of the mass, particularly on the right side, there is the formation of alveoli which approach more nearly normal thyroid acini.

In the final local recurrence the tumor is covered with a thin fibrous capsule. Next to this the tissue is composed of closely placed alveoli which show considerable variation in size and some irregularity of outline. There are large areas of necrosis, in which the stroma has lost all structure, but in which widely separated acini are still well preserved. Many of these are surrounded by a clear space. The tumor is very vascular. The alveoli contain a small amount of finely granular, unstained material, indicating some secretory activity in those acini which have lumina. The lining cells are cuboidal and contain considerable cytoplasm. Those which appear well regulated measure 14.4 by 10.04 micra and have nuclei with dimensions of 7.1 by 5.7 micra (Plate V, Fig. 55*a*). The nuclei of such cells are round and vesicular, with an easily seen reticulum upon which are deposited very fine chromatin granules, as well as a small number of larger ones. The majority of the nuclei are of this type. The cytoplasm of the acinar cells is rather coarsely meshed and usually considerably vacuolated, particularly about the nucleus. A rather large proportion of the nuclei are intensely stained and are irregular in outline (Plate V, Fig. 55*b*). The hyperchromatism of such nuclei is due chiefly to an increase in finely granular chromatin. Chromidiosis, leading to a decrease in hyperchromatism, is frequent (Plate V, Fig. 55*c*). No mitoses are seen.

In the cervical lymph gland invasions, necrosis is also extensive and complete, only the invaded marginal zones of the glands being spared. The lymphoid tissue is completely replaced by tumor tissue, except for a few small islands of lymphocytes just beneath the capsule. The tumor tissue is composed of very small irregular alveoli, most often in the form of round or elongated solid cell nests. The very small amount of stroma is richly supplied with large capillaries. Individual cell outlines are often difficult to determine and the nuclei are closely placed because of the small amount of cytoplasm. The predominating cells have a size of 7.4 by 6.4 micra, with nuclear diameters of 5.5 micra (Plate V, Figs. 56*a* and 56*b*). Giant nucleus formation leads to cells measuring 9.8 by 12.5 micra, whose nuclei measure 8.4 by 10.8 micra (Plate V, Fig. 56*c*). Hyperchromatism is much more marked than in the recurrence—the majority of the nuclei showing varying degrees of this condition. Many of the hyperchromatic nuclei are irregular in shape. Chromidiosis, while present, is not so active as in the local tumor. Only a few mitoses are seen.

In the lung metastases no lung tissue is evident. The surrounding lung tissue is slightly compressed, but shows no inflammatory reaction. The metastases are well defined, but in places there is actual invasion of the tissue of the alveolar septa. The tumor nodule is composed of cells arranged in large, irregularly shaped areas bounded by wide capillaries. Only here and there is there a slight indication of alveolus formation, without the production of any acini which even remotely approach those of the normal thyroid. There is no stroma except the minimal amount associated with the blood vessels. The cells show considerable variation in size. The average diameter of the majority of the nuclei is slightly less than in the recurrence or the lymph gland invasion—5.7 micra as compared with 6.4 micra. The cytoplasm forms a just barely visible rim about the nucleus. Moderate nuclear hypertrophy leads to the production of a considerable number of nuclei with an average diameter of 8.6 micra. In general, the cells of the metastases are well regulated, although scattered about there occur small, elongated cells with condensed, intensely stained nuclei (Plate V, Fig. 57). In the peripheral portions of the nodules a fair number of very hyperchromatic, slightly hypertrophied nuclei are found. There is some chromidiosis, which may, occasionally, be associated with vacuolization of nuclei (Plate V, Fig. 58). Mitoses are numerous. In many of the cells in various stages of karyokinesis there occur granules or rods of chromatin not included in the nuclear figure (Plate V, Figs. 59*a* and 59*b*).

*Tumor No. 7. A Lymphendothelioma, Primary in the Lumbar Vertebrae, with Extensive Metastases.*—The patient was a male, 45 years of age; he was admitted to the Lakeside Hospital, service of Dr. E. F. Cushing, June 16, 1901. He had been in good health until seven weeks before admission, when he was taken ill with pain in the abdomen, left side and back. On admission he walked with great difficulty and pain and a shuffling gait. Physical examination was negative, except for a considerable prominence at the side of the spinous processes of the third and fourth lumbar vertebrae. On July 20, 1901, a painful swelling at the sternal end of the left clavicle was first noted. Death occurred July 29, 1901. The clinical diagnosis was malignant tumor, primary in the lumbar vertebrae.

The autopsy was performed two hours after death. The growth was evidently primary in the third or fourth lumbar vertebra, the bony tissue of which was almost entirely replaced by a firm, greyish, translucent tissue. The growth also involved the body of the second lumbar vertebra and extended into the surrounding tissues, including the left psoas muscle.

There were extensive metastases involving the lumbar, mesenteric, gastrohepatic and bronchial lymph glands, liver, lungs, heart, left clavicle, sternum and three ribs. There were also smaller subcutaneous nodules in the skin over the chest, abdomen, back and left buttock. The metastatic growths were softer and evidently more cellular than the original growth, but otherwise they presented the same appearances.

In the primary growth the bone tissue has been almost entirely replaced by a rather dense fibrous supporting tissue, well supplied with blood and lymph vessels, and elongated alveoli containing very large cells. The cells are, as a rule, in rows of from one to six cells in width. There is no intercellular substance. The cell groups are, usually, sharply delimited from the supporting tissue, though in many places one or more cells are seen invading the latter. The cells in general are large, an average cell being 21.5 by 16.0 micra; some are huge giant cells, 65.0 by 30.0 micra and 90.0 by 20.0 micra being not unusual dimensions. Nearly all the cells of this, the oldest, portion of the tumor show marked increase of the nuclear material, even in proportion to the largely increased amount of cytoplasm. The nuclei of the smaller cells are, as a rule, single and hyperchromatic, with widely meshed reticulum and with one large or several smaller karyosomes. In some the chromatic material is in the form of fine granules scattered over the reticulum. Plastin nucleoli are present in some of the nuclei. Nuclear degenerations are common, and consist in chromatin diffusion and vacuolization. Giant nucleus formation is frequent. Ordinary direct division and nuclear budding are common. Mitoses are rare.

The huge giant cells show either active budding or the presence of numerous smaller nuclei, the result of budding. The cytoplasm, unless degenerated, is finely granular. In many large cells with nuclear hypertrophy and giant nucleus formation, in addition to nuclear degeneration, there is hyalin degeneration of the cytoplasm in whole or in part. Chromidiosis and nuclear resorption are not evident. The evidences of extension by means of the lymphatics are unmistakable. No tumor cells are to be seen in the blood vessels.

In the metastases the characters of the growth and of the cells differ with the age of the metastases. In the older lymph gland metastases and in the direct extensions of the tumor they are, in general, identical with those of the original tumor. In the smaller lymph nodes, omentum, clavicle, lungs, and liver, the characters of the growth and of the cells are quite different. That is, in the younger, more actively growing metastases the characters of the tumor are changed. The supporting tissue is much less developed, often quite cellular, the alveoli are more numerous, closer together, larger, round or oval in outline and of a more constantly uniform size. The cells are smaller (17.5 by 20.0 micra, 20.0 by 23.0 micra), oval in shape, with nuclei relatively but not excessively large. The nuclei are vesicular, with well marked membranes and linin meshwork. The chromatic material is usually in small masses and rarely in large karyosomes. Many nuclei contain one or more large plastin nucleoli. Very markedly hypertrophied and hyperchromatic nuclei, amitosis and nuclear budding are comparatively rare. Mitoses, contrary to what obtains in the primary growth and the old metastases, are numerous. Free in the cytoplasm in many cells are from two to ten large and small chromatic masses well without the division spindle—apparently dropped chromosomes, for there is no evidence of chromidiosis in resting cells. A relatively small proportion of the cells are of the giant cell type, with nuclei and cytoplasm showing all the changes described in the original growth. In certain areas multipolar mitoses are numerous.

Examples of rapidly growing tumors of the second group occur chiefly among carcinomata of glandular organs and sarcomata. The cells of these tumors exhibit regulatory processes in high degree. The most prominent are nuclear resorption, chromidiosis, amitosis and nuclear budding. We have noted a strong tendency for the cells of a given tumor to adopt and develop to a high degree a single method of regulation, sometimes, but not always, largely to the exclusion of others. Thus, in Tumors Nos. 8 and 9 the chief regulatory processes are chromdiosis and nuclear resorption, in Tumor No. 11 amitosis and nuclear budding, without chromidiosis, and in Tumor No. 10 all of these methods are prominent.

*Tumor No. 8. A Rapidly Growing Carcinoma of the Right Breast with Extensive Metastases in the Right Axilla.*—A woman, aged 31 years, was operated on February 26, 1908, by Dr. G. W. Crile at the Lakeside Hospital. Six months before, she had noticed a small mass in the right breast. This had increased in size very markedly in the past four weeks. On admission to the hospital the right breast was twice the size of the left.

The growth occupied a large portion of the breast and there were extensive but small metastases in the axillary lymph glands. Material was fixed in Flemming's solution and in saturated sublimate solution within five minutes after removal from the body.

In the breast tumor the growth is composed of closely placed alveoli containing oval and polygonal cells of the epithelial type, evidently of glandular origin, and supported by a rather cellular fibrous tissue stroma well supplied with blood vessels. The alveoli are usually oval, and in the older parts of the growth are rather large and completely filled with cells. In the younger parts, particularly at the extending margins, the alveoli are smaller, further apart and often lined by from one to three rows of cells and show central lumina.

As a whole, the cells have the appearance of being well regulated. Mitoses are numerous, except in the oldest portions of the growth. A type cell among dividing cells has a finely reticulated cytoplasm and an oval vesicular nucleus with a well marked reticulum. The nucleus has a fairly large karyosome and usually fine chromatin granules are present on the nodes of the reticulum. The cytoplasm of such a cell measures 15.0 by 10.8 micra, the nucleus, 10.0 by 6.75 micra. Cells with proportionately larger nuclei, both with and without increased amounts of cytoplasm, show a number of interesting phenomena.

In the cells somewhat larger than the type cell, the nucleus often possesses a very large karyosome, either round, oval or elongated. In these, various stages of karyosomic division, identical with those described in Tumor No. 3, are evident. The karyosome divides into two and sometimes three parts which are usually equal. If these karyosomes remain in the nucleus, the latter shows evidences of division and budding as in Tumor No. 3. In many nuclei, however, a young karyosome, or even two, often of considerable size, may be extruded from the nucleus as chromidia. In some cells, the karyosome extends from the nucleus through the cytoplasm and beyond the latter.

Cells of a size often smaller than the type cell show marked nuclear hyperchromatism. These nuclei may reduce themselves by chromidiosis, or the nuclei may degenerate with marked vacuolization of the enlarged karyosomes, leaving finally, after hyalin degeneration of the cytoplasm, free, shrunken and vacuolated karyosomes, as one of us (Howard, 1908) has described for *Actinosphærium*, and as so often occurs in Tumor No. 2.

In many cells with hypertrophied, hyperchromatic nuclei, the protoplasm reaches considerable size. The cytoplasm of a cell of this variety measures 20.0 by 13.5 micra, the nucleus 15.0 by 10.8 micra. Such cells may reduce their nuclear material very greatly by chromidiosis (Plate V, Figs. 60, 61 and 62*a*), after which mitosis may occur (Plate V, Fig. 62*b*). The whole nucleus may dissolve into chromidia (Plate V, Fig. 63). The nucleus may become of giant size (as in a cell whose cytoplasm measures 22.0 by 10.0 micra, and whose nucleus measures 19.25 by 8.4 micra), with or without budding. The nuclei and cytoplasm of such cells often show degenerative changes and even necrosis. Chromidiosis does not occur in cells with giant nuclei. The throwing off of nuclear buds by hypertrophied, hyperchromatic or even giant nuclei may be followed by mitosis of the mother nucleus, as in Tumor No. 4. The growth of the cytoplasm in cells with large nuclei may be so marked as to produce a cell measuring 41.5 by 30.4 micra.

The mitoses are usually normal in appearance, but in many the amount of chromatic material in the division figure is excessive—hyperchromatic mitosis. In many such cells the division is abortive and the chromosome mass breaks up into larger and smaller masses. Multipolar mitoses are occasionally found. Though the cells in the main are fairly well regulated, there are evidences of considerable nucleus-plasma upset on the part of some cells, as shown by the nuclear hypertrophy, hyperchromatism, giant nucleus formation, nuclear budding and various degenerations of nuclei, hyalin and vacuolar degeneration, overgrowth and necrosis of the cytoplasm of some of the cells.

In the lymph gland metastases the alveoli are, as a rule, large, closely packed together, with relatively little supporting tissue. There are but few alveoli with central lumina. The growth is evidently rapid; there are very numerous mitoses, which are, as a rule, normal. The type cell is of the same size and structure as in the original growth. Nuclear hypertrophy, hyperchromatism and giant nucleus formation are present, but not so frequent. The cells do not reach such large size, and there is not so great a mortality from physiological degeneration. Giant cells are rare. Direct division and budding are not infrequent and are always preceded by very definite binary and trinary divisions of the karyosome. Chromidiosis is very frequent and here, too, the same relation to karyosomic division is also seen, and one or more of the products of this division may be cast out. There is a considerable number of cells with large plastin nucleoli in various stages of growth. Many of the cells in mitotic division contain chromidia. There are some hyperchromatic mitoses, and in many of these the division is abortive and the figure may disintegrate. On the whole, in the metastases the growth is rapid, the regulation is good and the mortality of the cells is low. The marked influence of chromidiosis as a factor in regulation is the most important feature of this tumor.

*Tumor No. 9. A Metastasizing Carcinoma of the Lung.*—A colored woman, aged 37 years, gave a history of having "caught cold." There was some vomiting during the early weeks of her illness. Death occurred seven weeks after the earliest symptoms.

At autopsy the greater portion of one lung was found transformed into grayish red tissue. The other lung and the pleuræ of both sides were involved. All the abdominal organs showed numerous small metastases and both layers of the peritoneum were studded with small nodules.

Microscopically the tumor tissue of the lung showing most involvement is composed of very irregular, gland-like alveoli embedded in a dense fibrous stroma, which is well supplied with blood vessels. In most alveoli the lining cells are heaped up in several layers, forming short papillomatous ingrowths into the alveolar lumina. The alveoli vary in size and in outline.

The individual cells of the primary tumor vary considerably in size. A cell diameter of 10.2 micra, with a nuclear diameter of 6.6 micra, may be taken as about the average. Of cells differing in size from this average the greater portion are slightly larger. In such cells the nucleus has a fine reticulum upon which are deposited very fine chromatin granules, with an occasional larger chromatin mass. The cytoplasm is closely meshed. The greater portion of the cells in the primary tumor have hyperchromatic nuclei whose outlines are often somewhat irregular. Depression, as evidenced by hyperchromatism and giant nucleus formation, is marked, although the tumor shows at the same time great regulatory powers, as indicated by chromidiosis, nuclear budding and normal mitosis. Many cells, however, are unable to overcome the depression and die with cytoplasmic vacuolization and fragmentation of hyperchromatic nuclei.

In the metastases the stroma is quite prominent, but varies somewhat in amount in the various organs. The acini are smaller than in the primary growth and show much more intra-acinar papillary ingrowth of the epithelium. Mitoses are numerous. Although there is considerable variation in the size of the cells, not so large a proportion of cells is hyperchromatic as is the case in the primary tumor. Type cells (Plate V, Fig. 64) measure 15.0 by 7.8 micra and have nuclei measuring 6.4 by 7.8 micra. Large cells with well regulated, vesicular nuclei are, however, numerous. Hyperchromatism is seen in nuclei of the type cell size (Plate V, Fig. 65) and in giant nuclei (Plate V, Fig. 66). Such nuclei may be so loaded with fine chromatin granules that the reticulum is almost completely hidden (Plate V, Figs. 65 and 66). In other cases there are, in addition, larger chromatin masses. More rarely the excess of chromatin is not distributed uniformly throughout the nucleus, but is deposited in a small number of larger bodies (Plate V, Fig. 67). Budding is not so frequent in the metastases as in the primary tumor, but chromidiosis is very active. The amount of chromatin extruded may exceed that still remaining within the nucleus (Plate V, Fig. 68) or almost the entire nucleus may be transformed into chromidia (Plate VI, Fig. 69). In some cases chromatin extrusion, although present, is unable to restore the proper balance and the cytoplasm becomes markedly vacuolated. An occasional hyperchromatic nucleus is vacuolated (Plate VI, Fig. 70).

*Tumor No. 10. A Giant Cell Sarcoma of the Neck.*—A white male, aged 43 years, three months before admission to the Lakeside Hospital began to be troubled with neuralgic pains in the left arm. Five weeks before admission he noticed a small swelling on the left side of the neck. The mass grew rapidly and there had been a loss in weight of over twenty pounds since the beginning of symptoms. An extensive operation was necessary for the removal of the tumor.

The tumor is composed of irregularly shaped cells, running between which is a small amount of connective tissue stroma. Broader bands of fibrous tissue carrying thin-walled blood vessels divide the tumor tissue into areas of varying size and shape. Even with very low magnifications one is struck by the variation in the size of the nuclei and by the intense hyperchromatism of the larger ones.

The nuclei of the smaller cells do not contain an excessive amount of chromatin. Such well regulated cells vary in size from 18.2 by 9.5 micra to 12.8 by 9.5 micra. The nuclei show corresponding variations, 11.4 by 4.0 to 7.4 by 5.4 micra, so that the individual cells contain considerable cytoplasm. The distribution of the chromatin within the nuclei varies. In some, small granules distributed about upon a closely meshed reticulum bring the latter into view. Finely and more coarsely granular chromatin is also deposited upon the inner surface of the nuclear membrane (Plate VI, Fig. 71). In other nuclei the reticulum can hardly be distinguished and the chromatin occurs in the form of large masses applied upon the membrane and lying free within the nucleus (Plate VI, Fig. 72). In the hyperchromatic giant nuclei similar differences also occur. Some nuclei are loaded with finely granular chromatin (Plate VI, Fig. 73). In others the excessive amount of chromatin is gathered into very large round or oval masses (Plate VI, Fig. 74). Chromidiosis is marked and occurs in most of the cells which show even only a slight increase in the amount of nuclear chromatin. The extranuclear chromatic material may be in the form of very minute granules, often present near and upon the outer surface of the nucleus (Plate VI, Fig. 74), or in the form of large as well as small granules scattered throughout the cytoplasm (Plate VI, Fig. 75). The larger chromidia may be vacuolated. In a few cells the cytoplasm has a diffuse, faint brownish tinge due to the presence of minute granules of pigment. In such cells the nucleus is usually not hyperchromatic and the presence of fine particles of chromatin in the cytoplasm indicates that the nucleus has reduced itself by chromatin extrusion (Plate VI, Fig. 76).

In spheroidal cells with an average diameter of 12.8 micra the cytoplasm is coarsely vacuolated and both relatively and actually large in amount (Plate VI, Fig. 77). The nuclei, which measure 4.3 micra in diameter, are so intensely hyperchromatic as to look almost like solid balls of chromatin. When chromidiosis occurs in such cells (Plate VI, Fig. 78) the nucleus stains more faintly, but we have never seen nuclei of this type in which there was a complete return to the vesicular character of well regulated nuclei.

Actual resorption of chromatin, with or without solution of the nuclear membrane, also occurs in this tumor. In a nucleus which must have had originally a structure like that of Fig. 72 (Plate VI), the membrane is intact, but the chromatin masses stain very faintly and portions of the cytoplasm take a diffuse chromatin stain (Plate VI, Fig. 79). This same process occurs also in cells with small, solid, round, hyperchromatic nuclei (Plate VI, Fig. 80). In other nuclei, in addition to the decrease in stainability of the chromatin, there is partial disappearance of the nuclear membrane (Plate VI, Figs. 81 and 82).

Examples of amitosis (Plate VI, Fig. 83) and of nuclear budding (Plate VI, Fig. 84) are very numerous. Some cells may show chromidia as well as buds (Plate VI, Fig. 84). Before the process of budding has reached so advanced a stage as that shown in Fig. 84, the giant nuclei in which the process has just begun are still very hyperchromatic.

In this tumor are found nuclei of a kind which we have seen in no other neoplasm. They may show one or two large protuberances covered with a distinct nuclear membrane (Plate VI, Figs. 85 and 86). Because of the retention of the outlines of the original nucleus (Plate VI, Fig. 85) these bud-like outgrowths give the impression of having been very suddenly formed. This is further accentuated by the streaming of the chromatin within the buds, leading to the formation of chromosome-like strands. Concerning the end result and purpose of this process we are not quite sure. Mitotic figures occur, but are not numerous.

The chief points of interest in this tumor may be summarized as follows: There is marked depression of a large proportion of the cells, as evidenced by the intense nuclear hyperchromatism. The depression does not, however, lead to any very striking cell mortality. Very little evidence of cellular degeneration and death is seen, except the excessive nuclear resorption illustrated by Figs. 79 to 82 (Pate VI). That the depression does not have more serious consequences for the individual cells is explained by the very active regulation by means of marked chromidiosis, nuclear budding, chromatin resorption, direct division and mitosis.

*Tumor No. 11. A Rapidly Growing Carcinoma Occurring in a Nursing Breast, Occupying the Whole Breast and Invading the Underlying Muscle; Large Metastases in the Axilla.*—Three months after the birth of a child, and while nursing the latter, the right breast became painful and swollen. It was treated as a mammary abscess. A week before removal of the breast, and two months after the first symptoms, incision emitted a considerable amount of puriform material.

The growth, which occupied the whole breast, had a central cavity about the size of a small orange. The cavity had firm walls and contained a small quantity of puriform material. The axillary glands varied from 3.0 to 10.0 cm. in diameter.

Sections taken from the older portions of the growth are composed of very large and long alveoli of round, oval cells of the epithelial type, supported by a relatively small amount of fibrous tissue stroma. There is no semblance of an attempt at the formation of glands or ducts. The tumor cells vary much in size. For the most part they are large, often giant in size, with hypertrophied and often giant nuclei. Some of the giant cells have a large diameter. The nuclei are for the most part vesicular, with one or more large karyosomes. Amitosis and nuclear budding are present in nearly all of the cells. Many cells are filled with from three to twenty or thirty nuclear buds. Degeneration and extrusion of nuclear buds are not infrequent.

In some giant cells, after nuclear budding, mitosis of the mother nucleus, as described in Tumor No. 4, may occur. In some of the giant cells containing nuclear buds, with a large nucleus still throwing off buds, several, in one case four, nuclear buds are in various stages of mitosis, with definite spindles.

While most of the giant cells are evidently the result of excessive growth of the cytoplasm of individual cells, some are clearly due to plasmogamy. A large proportion of the cells are in hopeless depression, and show vacuolar and hyalin degeneration of nuclei and cytoplasm. The mortality from physiological degeneration is high in this portion of the growth.

Mitosis is infrequent and, where present, the mitotic figures are hyperchromatic and the chromosomes are large. A large proportion of the mitotic figures are multipolar. Dropping of chromosomes is not infrequent. Degenerated mitotic figures, sometimes with vacuolar degeneration of some of the chromosomes, are met with.

There is no inflammatory exudation in the tumor. The large area of necrosis is sharply marked and evidently vascular in origin.

In the peripheral portions of the growth and in the metastases, the picture is quite different. The alveoli are smaller, and the supporting tissue is more in evidence. The tumor cells are smaller and much better regulated. Giant cells and nuclear hypertrophy and hyperchromatism are less common. Mitoses are very numerous and the division figures are of a more normal type. They are present in every stage. Some multipolar mitoses are met with, but relatively much less frequently than in the older portions of the growth.

## IV. THE CORRELATION OF THE GROWTH PHENOMENA OF TUMOR CELLS WITH CERTAIN FACTS OF GENERAL CELLULAR BIOLOGY.

### GROWTH AND DIFFERENTIATION. ANAPLASIA AND METAPLASIA.

One of the most striking characteristics of protoplasm is its inherent capacity for growth and differentiation. In normal growth and development, the growth rate and differentiation of protoplasm follow definite laws. With proper food and environment, growth proceeds at definite rates which vary for different stages of development and may be modified experimentally, as has been shown. Protozoan cells grow to a certain size and divide, and the daughter cells repeat these phenomena. In the developing metazoön, growth and cell divisions are rapid, with a minimum amount of differentiation and, after repeated haltings and startings, the animal and its organs attain a certain rather definite size, when growth and cell divisions are arrested as if automatically, and differentiation corresponding to the function of the various component cells is perfected. Thenceforth, further growth and cell divisions occur only under certain definite conditions: (1) for renewals, to replace cells and parts; (2) under physiological stimulation, producing the hypertrophies and hyperplasias, the repair of wounds, etc., which latter may, in essence, be regarded as renewals; (3) proliferations incited by certain stimuli from without, resulting in inflammatory new formations; (4) the formation of sex cells; and (5) tumor formation.

The bulk of evidence is in favor of the idea that growth is slowed, curbed or completely arrested by certain factors residing in the individual cells and to some degree associated with cell differentiation, which cause, in effect, a hindrance to further growth. This hindrance may be almost complete, as in the case of nerve and striated muscle cells, or more or less readily overcome, as in epithelia and mesenchymal cells.

Each variety of cell leaves division with a given amount of dynamic energy, the production of which is due to cellular metabolism and the expenditure of which is divided in varying proportions between growth and functional activity. In the normal cell, there are limits within which the amount of dynamic energy which it can produce varies. In the cells of hypertrophies, hyperplasias and benign tumors, while the amount of dynamic energy is increased to a maximum within normal limits, its distribution between growth and function remains in approximately the same proportion as in the normal cell. In the cells of malignant tumors, on the other hand, the dynamic energy is not only increased in amount and does not wear out, but is diverted largely to growth rather than to specialized functional activity.

The setting aside of the limits of energy production and the disturbance of its normal proportionate distribution and expenditure between growth and function constitute the main and essential differences between the cells of malignant tumors and other cells. This conception is partly reached by Hansemann (1893) in his anaplasia theory and by R. Hertwig (1904) in his idea of the difference between cytotypic and organotypic growth in relation to tumor cells.

According to our conception, the essential factor in the restraint or hindrance to continuous growth on the part of individual cells is the inherent tendency of protoplasm to preserve the proper or normal balance between the distribution of the dynamic energy produced by the cell between growth and functional activity, as exhibited chiefly in differentiation and secretion.

In the renewals of lost parts, in the physiological hypertrophies and hyperplasias, and in the inflammatory new formations, in short, in all examples of renewed and accelerated rates of growth due to known growth stimuli, this law applies. In all these processes growth is usually rapid, but, as a general rule, in inverse proportion to its rapidity, differentiation is perfect or imperfect. There is a marked tendency for the cells to breed true and to fully differentiate into normal tissue, and to recover the proper balance in the distribution of their dynamic energy. In exceptional instances this recovery is incomplete or even perverted. In the latter condition, metaplasias arise.

The thyroid furnishes a remarkable illustration of the application of this law to the variations in the characters of growth under different influences. In this gland, whose cells are under good control, after renewals for wear and tear and after the excision of parts, growth halts with the achievement of perfect differentiation when renewal is complete.

The studies of our colleague, Marine (1907 *a* and *b*, 1908, 1909 *a*, *b*, *c* and *d*), have shown that, under conditions otherwise constant, the withdrawal of a single substance, iodin, from the diet, is followed by active growth of the glandular tissue of this organ in direct proportion to the amount of this element withheld. A slight deficiency of iodin is followed by a true hypertrophy, with an increase in the size of the acini and of the individual epithelial cells, and a greater deficiency of iodin by a marked true hyperplasia with newly formed acini with relatively large cells. In the hyperplasia there may be produced an enormous amount of new tissue, the physiological value of whose secretion to the organism is inverse to the degree of hyperplasia. The absence of iodin, relative or absolute, acts as a powerful growth stimulus under the influence of which the cell increases markedly its production of dynamic energy, which is, however, diverted from normal physiological secretory functional activity to growth and division. The active growth and division of the thyroid cells under these conditions may result in profound depression, in which so many of the cells are lost that myxedema results (personal communication from Doctor Marine). Marine has further shown that the administration of iodin in proper doses during any period of thyroid hypertrophy and hyperplasia, short of profound depression, is followed by arrest of growth and resumption of normal functional secretory activity, colloid production, and the reversion of the gland to a condition approaching the normal structure, colloid goiter, with a return of the cells to their normal shape and size, and the restoration on the part of the tissue of an iodin content as great as or greater than normal.

Proceeding from thyroid hyperplasias, as they occur in nature, in which the cells recover from or avoid depression by various regulatory processes, and grow rapidly, there occur adenomata and carcinomata, over which iodin has no control.

In the case of the hyperplasias, the absence of a single substance, iodin, and the attempt of the gland as a whole to produce as efficient as possible a secretion in spite of the lack of this necessary element, act in conjunction as a very powerful stimulus, as the result of which there is a marked increase of the cellular dynamic energy. The continuous action of the stimulus, due to the persistent deficiency of iodin, leads to the diversion of an abnormal proportion of this energy from physiological function to growth. Removal of the stimulus at any stage of the hyperplasia, by the administration of iodin, results in the restoration of a more or less perfect balance in the distribution of this energy between growth and functional activity. In proportion to the degree to which this resumed functional activity follows normal lines, growth is arrested.

When, however, the stimulus acts to an excessive degree or for too long a time, the balance in the distribution of the increased dynamic energy between growth and functional activity is permanently altered, growth becomes unlimited and the result is a malignant tumor over which iodin has no effect.

And, likewise, in tumors elsewhere, the initiation and progress of the process are to be explained by the accession on the part of the cells of increased energy production and by an improper correlation of the expenditure of the latter between growth and functional activity.

Hitherto, in our discussion of tumor growth, we have purposely left out of consideration cell division, which we think the work of R. Hertwig (1903 *a* and *b*) and of Popoff (1908) has proved to be the direct result of growth. When, as the result of growth, a cell reaches a certain size and the proper nucleus-plasma tension is attained, division occurs. Division, as we have indicated, is a regulatory process. The present problem is not so much, why does division occur? as, what are the causes of the growth of protoplasm that lead to division and make it important or even necessary to the life of the cells?

The varying capacity for division possessed by different cells when incited to growth has a profound influence upon the course and fate of tumors. Unless the division capacity of the cells is great and the division factors powerful, the growth, however great the stimulus, is limited. These properties, as we have already indicated, vary with different cells.

When the incitant necessary to stimulate excessive growth acts upon the cells of a part and is accepted, the course and fate of the resulting tumor must depend upon: (1) the divisional capacity of the cells; (2) the nutrition; and (3) the avoidance of depression and the regulatory processes available to and utilized by its cells.

It is evident that beyond a certain point the growth rate is determined by the division rate, for unless the cells can divide, growth becomes arrested. The division rate is dependent upon the division factors of the cell itself. These may rise or fall in strength in a given tumor. If they are not powerful enough to produce division of some type, the cell vegetates or goes into depression and often dies. The mortality of cells from depression is often great, even in rapidly growing tumors. Death of large foci of tumor tissue is usually traceable to vascular changes and is, therefore, due to lack of nutrition. It is probable that retrogression of tumors is due to these two factors, the death of individual cells from depression and of masses of cells from lack of nutrition, together with certain others, such as hemorrhage and the production of lytic and other antibodies.

Tumor formation is associated with varying degrees of loss of differentiation of the constituent cells. As a general rule, rapidity of growth and increasing loss of differentiation go hand in hand. Whether this association means that slowly growing tumors show greater degrees of differentiation because the time between divisions of individual cells is long enough to permit of differentiation or that the acquiring of an increased divisional capacity has destroyed, to a certain degree, the potentiality of differentiation, is difficult to decide. The rule that growth rate and loss of differentiation go hand in hand is not an inflexible one. Krompecher's basal cell epitheliomata of the skin usually have a slow rate of growth, yet the individual cells tend to retain the morphological characteristics of the basal cells of the epidermis. Other epidermal tumors, of a much more rapid rate of growth, may show considerable differentiation of individual cells. In very rapidly growing malignant tumors, the cells, so long as individual cells are formed, rarely lose all differentiation. The cells may be morphologically young, but are rarely true, undifferentiated embryonic cells. The work of Mallory (1908) and others has shown that the cells of such tumors form fibrils characteristic for the adult normal cell from which the tumor was derived. Gland cell tumors may show a certain degree of secretory activity.

Differentiation, then, seems to be the morphological expression of specialized cell function or, at least, of functional potentiality. Structural modifications are the mechanism by means of which the nucleus controls cell activity. Differentiation is a process through which nuclear energy finds an outlet and by means of which cell depression due to nuclear overgrowth may be in part prevented.

No matter how rapid the rate of tumor growth and how great the loss of differentiation, individualized cells are produced. Mall (1902) has shown, however, that connective tissues are derived from a syncytium. He leaves open the question as to whether the mesenchyme was ever composed of individual cells or whether it was not from its very beginning a syncytial structure. From the syncytium the individual cells and the intercellular substances of differentiated connective tissues are derived. Although the connective tissue tumors with which we are acquainted are composed of individual cells, which may show very great loss of differentiation, there arises the question of the theoretical possibility of the occurrence of tumors in which the power of differentiation has been lost to such an extreme degree that not even individual cells are produced—tumors, other than those derived from the placenta, testis, or ovary, composed of syncytium. Associated with this question is the further one as to the fate and the rate of growth of such a tumor. According to Mall, in the syncytium from which normal connective tissues are derived, the rate of protoplasm growth exceeds that of nuclear growth. According to our interpretation of this observation, it is not until the greater bulk of the plasma has been used up, by the process of differentiation, in the production of intercellular substances that the cells, now individualized, show such a relation between nucleus and cytoplasm as permits them to attain their normal division rate.

Since connective tissue cells do often revert to so young a condition as that met with in round cell and spindle cell sarcomata, one must grant the possibility of even further reversion and of the occurrence of a syncytial connective tissue tumor. And if this syncytial tumor mass is incapable of a degree of differentiation sufficient to produce intercellular substance or individual cells, it ought, theoretically, to have an extremely slow rate of growth. One would then have a striking exception to the rule of the association of rapid growth and loss of differentiation—an exception in which extreme loss of differentiation is associated with very slow growth. Tumor No. 1 is an example of such a neoplasm.

The future possibilities of such a tumor are interesting and would seem to be dependent very largely upon the differentiation capacity of the tumor tissue. If a slight degree of differentiation is attainable with the formation of individual cells with the nucleus plasma relation of spindle sarcoma cells, there is given the possibility of the transformation of a slowly growing, relatively benign tumor into a rapidly growing malignant one. A greater degree of differentiation along more normal lines might lead to the formation of intercellular connective tissue which might have the structure of fibrous tissue, cartilage or bone. The result might be a benign connective tissue tumor or a nodule of normal tissue with a structure either similar to or different from that of the surrounding tissue. There is the final possibility of complete inability to produce individual cells or intercellular substance. The end result of such a process would be atrophy of the tumor tissue.

The tumor under consideration is especially important because of the emphasis that it gives to the loss of the power of differentiation. In most tumors anaplasia is only relative—there is rarely the formation of true embryonic tissue. Moreover, the anaplasia may be only a temporary condition in the life of any individual tumor cell. In most tumors comparison of the youngest and oldest cells shows that the cells possess to a considerable degree the property of advancing differentiation. By a loss of differentiation in a connective tissue tumor so extreme as that in this tumor, there is given the possibility of advancing differentiation which may lead to the formation of a connective tissue of a type different from that from which the tumor originally came.

It is well established that different degrees of lack of differentiation, that is, different grades of anaplasia, are associated with cell depression. From this state of anaplasia, after recovery from depression and upon the resumption of growth and cell division, metaplasias often proceed. A familiar example of this is found in certain chronic inflammatory processes in the choroid, lungs, lymph glands, arteries and heart valves, in which in the newly formed fibrous tissue, after depression and anaplasia, there is a period of renewed growth with aberrant differentiation or metaplasia, resulting in the formation of cartilage and bone. Several authors have described the formation of mucous cells, striated muscle and even ganglion cells in the thymus, and Marcus (1908) has pointed out that this occurs at a period when some of the thymus cells are recovering from profound depression and are anaplastic. Marcus further correlates these phenomena of the thymus cells—their capacity for metaplasia after recovery from depression—with the various histological differentiations found in dermoid cysts. In the same manner, from such a tumor as the one under discussion (Tumor No. 1), or from any similar completely anaplastic tissue, on the accession of renewed growth and division capacity, there might arise not only a complicated mixed tumor, such as are so common in the urogenital tract, but dermoid tumors and even the so-called chorio-epitheliomata of the testis. In the light of the foregoing, it is entirely unnecessary to assume the origin of such tumors from hypothetical embryonic rests, either simple or compound. The existence of the latter, in adult tissues, R. Hertwig (1904) has shown, on theoretical grounds, to be impossible.

Therefore, in conclusion, it may be said that the growth rates of tumors vary not only with the growth capacities of the tissues from which they spring and the capacity of the cells of these tissues to divide, but must be influenced further by the release from hindrances to growth and by the action of new growth stimuli; and that after the tumor growth has been initiated, the growth rate must be governed by the capacity of the cells for differentiation and for other regulatory processes, as well as by nutrition.

## VARIATIONS IN GROWTH RATE IN THE DIFFERENT TUMOR GROUPS.

### *Benign Tumors.*

The slowly growing benign tumors, springing from smooth and striated muscle, from the supporting tissues in general and from epithelial tissues, are chiefly characterized by differentiation of their cells, which is perfect or nearly perfect. The cells of these tumors differentiate as do the tissues in hypertrophies and hyperplasias. The growth and division rates of the cells are uniformly more rapid than those of normal tissues, differentiation is good and evidences of depression are lacking. The nucleus-plasma relation is permanently fixed, so long as the tumor remains benign, at a level different from that of normal tissues. They seem to bear the same relation to normal tissues that *Frontonia* individuals cultured at warm temperatures bear to those grown in the cold. These tumors are to a certain degree self limited and do not, as a rule, form metastases, except by accident, that is, by invasion of a vein and by implantation in contiguous tissues.

### *Malignant Tumors of Slow Growth.*

In the slowly growing malignant tumors, especially in the sarcomata composed of smooth muscle and fibrous connective tissue, and in certain epithelial tumors, especially those springing from stratified epithelia, differentiation is often well marked, but usually short of perfect. In such tumors there are commonly evidences of depression from imperfect cell regulation. It is also likely that the incitants to cell division are not very active.

Study of Tumor No. 1 shows, among other things, that even lack of differentiation does not necessarily result in rapid growth. Imperfect cell regulation may be a potent cause of slow growth, as is shown by the findings in Tumor No. 2, in which there is a heavy mortality among the tumor cells from depression and arrest of mitotic division, without proper differentiation and other modes of regulation.

### *Malignant Tumors of Moderately Rapid Growth.*

In tumors of moderately rapid growth, in our experience, the growth rate is either uniform with well marked differentiation of the cells, often accompanied by secretory activity—as in the typical adenocarcinomata of the intestines and uterus; or a slow growth rate is followed by a more rapid growth rate, in which there are evidences of the accomplishment of regulation by chromidiosis, amitosis and nuclear budding (the latter associated with degeneration and extrusion of nuclear buds), not infrequently followed by mitosis; or lastly, with considerable evidence of regulation and rapid division, many of the cells fall into fatal depression. In tumors of the latter category, a large part of the gain in cells is lost by depression, physiological degeneration, and death of their cells.

### *Malignant Tumors of Rapid Growth.*

The tumors of rapid growth spring from the same tissues which give rise to tumors of slow and moderately rapid growth. The variations in the strength of the unknown incitants to growth and division cannot, of course, be estimated, but *a priori,* they must play a large part in the determination of the rate of growth. As has long been known, in these tumors differentiation is poor, and evidences of physiological secretion are absent. Both of these factors, while giving greater freedom to the cells for growth, on the other hand favor the occurrence of depression. Hence, though the cells of these tumors are in general well regulated, with a nucleus-plasma relation within physiological limits, cell depression occurs. On this account, in many cells division is no longer possible and the mortality of individual cells, isolated and in groups, usually in the older portions of the tumors, from physiological degeneration is often heavy.

The most conspicuous characteristics of these tumors are the large numbers of mitoses and amitoses, indicative of great growth and division energy and of the regulatory capacity of their cells. Taking an individual tumor as a whole, while hypernucleosis may be common, giant cells with single giant nuclei and multiple small nuclei are comparatively rare. The cells dying of depression are usually small cells with hypertrophied and hyperchromatic nuclei similar to thymus cells.

The cytoplasm shows marked evidences of a well developed capacity to reduce nuclear material by nuclear resorption and chromidiosis, followed by extrusion or breaking down of the chromatic material in the cytoplasm, occasionally with pigment formation. The dropping of chromosomes from hyperchromatic division figures is not of unusual occurrence.

Rapidly growing tumors which are exceptions to the general rule and have numerous giant cells are not infrequently met with. These are well illustrated by Tumors Nos. 10 and 11, the first being a sarcoma, and the second, a carcinoma. In Tumor No. 10, in which growth was very rapid, there is a very considerable development of giant cells and depression is marked. But regulatory processes, amitotic division, budding and chromidiosis, are conspicuous and are sufficient to save many of the cells from death, though few recover the capacity for mitosis. In Tumor No. 11, though chromidiosis does not occur, amitosis, budding, with nuclear extrusion, and mitosis of mother nuclei thereafter, are common.

## DEPRESSION IN TUMOR CELLS.

A review of the tumors described in this paper makes it evident that depression may and often does occur in the cells of many tumors.

In the slowly growing benign tumors with perfect or nearly perfect differentiation, depression is not in evidence.

In some of the slowly growing malignant tumors it is often marked. For instance, in the so-called basal cell carcinomata with very poor differentiation it is great. In many slowly growing fibrosarcomata and in carcinomata, especially in those springing from stratified epithelia, the slow growth is evidently due largely to the marked depression of the cells (Tumor No. 2). The depression is so marked that division is arrested.

In many tumors of moderately rapid growth depression of many or even most of the cells, especially in older areas, is often the most prominent feature; while in tumors of rapid growth many of the cells show evidences of varying degrees of depression.

The depression of tumor cells shows all the marks and characteristics of depression of protozoa, sex cells, thymus cells and of certain other metazoan cells, as described by R. Hertwig and his pupils. In so far as the nature of tumor cells coincides with that of the above mentioned cells, our findings are in complete accord with theirs.

Rapidly repeated divisions are followed in certain protozoa, in sex cells, in thymus cells and in many tumor cells by a depression in which the most marked feature is an upset of the nucleus-plasma relation in favor of the nucleus. In certain protozoa, other causes, such as overfeeding or change of temperature, may bring about the same result. In protozoa whose functional activity and growth and division rates are increased (overfeeding), the same overgrowth of nuclear material and degenerations of nucleus and cytoplasm are produced. Therefore, the causes of depression in all these types of cells are doubtless closely related, if not identical; at any rate they produce the same effects. Often in tumors of moderately rapid and of rapid growth, just as in protozoa in overfed cultures, the cells undergo alternate waves of depression and recovery with renewed capacity for multiplication. In some of the cells of certain tumors (Tumor No. 10) in which chromidiosis and nuclear resorption are very well marked, we have observed a form of depression quite the reverse of the common type and in which, due to the excessive elimination and destruction of nuclear material, the nucleus-plasma relation is upset in favor of the cytoplasm (Plate VI, Figs. 77 to 82). This brings about a condition of the affected cell analogous to that caused by hyperfunction, but the essential cause here is probably the development on the part of the cytoplasm of an excessive capacity for breaking down nuclear material

The two most conspicuous results of depression in tumor cells are curbing or arrest of capacity for mitotic division and the occurrence of physiological degeneration and death unless depression is relieved.

Apparently the most important factor concerned in the loss of the capacity for mitotic division in tumors of moderately rapid and of rapid growth is the inability of the division factors of the cells to accomplish successfully indirect division of the excessively large and hyperchromatic nuclei; that is, to inaugurate division and to divide the hypertrophied chromosomes. It is evident that Marcus' explanation of the causation of heterotypical mitoses in sex and thymus cells applies to tumor cells as well.

The nuclear overgrowth in tumor cells leading to depression is due, as in overfed *Actinosphærium eichhorni,* partly to excessive growth of nucleolar substance and partly to the taking up by the nucleus of an excessive amount of fluid from the cytoplasm. The influence of the latter factor, especially in markedly hypertrophied and giant nuclei, is clearly shown by the increase in the size of the spaces of the nuclear meshwork and by the frequent rupture of the latter. Of these two factors, the first is undoubtedly the primary and most important in tumor cells, for in the typically depressed nucleus, the great excess of nucleolar substance, with or without chromatin, is the striking feature.

## THE REGULATORY PROCESSES IN TUMOR CELLS.

### *Chromidiosis and Nuclear Resorption. The Fate of Chromidia.*

In the foregoing pages, the influence of a slow and regular growth rate, of cell division, of differentiation, and of functional activity as regulatory factors in tumor cells have been elaborated. It has been pointed out further, that chromidiosis and nuclear resorption are often resorted to by tumor cells, and that tumor cells which can attain to these two regulatory processes have a distinct advantage. They occur chiefly in rapidly growing tumors, in the metastases and at the spreading borders of tumors of moderately rapid growth. These two processes play the same effective rôle in tumor cells as in protozoan, sex and thymus cells, in preventing and relieving depression by restoring a proper nucleus-plasma relation, which may and often does allow mitotic division to follow.

The fate of chromidia is extrusion or disintegration in the cytoplasm, with or without pigment formation. Our observations on the formation of pigment from chromidia in tumor cells confirm those of R. Hertwig (1904) and of Howard (1908) on pigment formation in *Actinosphærium eichhorni,* and of Rössle (1905) on pigment formation in the cells of melanomata. We have not, however, found evidence of pigment formation from nuclear material within hyperchromatic nuclei of tumor cells. The breaking down of chromidia into pigment in tumor cells is of comparatively rare occurrence, except in those that spring from cells normally capable of pigment formation, that is, chromatophores. Perhaps it is largely on account of the power of their cells to break down excessive nuclear material with pigment formation that the rapid growth so characteristic of melanotic tumors is due.

### *The Dropping of Chromosomes.*

Besides the extrusion of chromidia from the nuclei of resting cells, we have observed the occurrence during mitosis of a phenomenon which must, we think, be ascribed to the same category as the chromidiosis of the resting cell, and classed as a regulatory process, though accomplished in a passive way. We have observed in rapidly growing tumors, in a large number of cells in the prophase and in the metaphase of mitotic division, the occurrence of fine granules and coarse, often irregular masses, of chromatic material, that is, portions of chromosomes lying entirely without the planes of the spindle. Sometimes, no doubt, these masses represent chromidia extruded from the nuclei before division began. But in other cases, from their situation, size, and general arrangement, there is no doubt that they represent chromosomes and portions of chromosomes which have either been dropped from or not included in the division figure. A nucleus hypertrophied and hyperchromatic within the limits in which division can be inaugurated starts mitotic division with hypertrophied chromosomes. The energy of the division factors is not powerful enough to pull the whole mass of chromosomes into the figure and, as division progresses, chromosomes or portions thereof are left out (as described in Tumors Nos. 6 and 8, Plate V, Figs. 59*a,* 59*b,* and 62*b*). There is no reason for thinking that these chromatic masses represent accessory chromosomes in the usual sense.

### *Multipolar Mitosis.*

It may be suggested in this connection that the phenomenon of multipolar mitosis is to be regarded in its results, at least, not as a pathological, but, in a passive fashion, as a regulatory process. Its occurrence in tumors is limited to cells with hypertrophied and hyperchromatic nuclei and a considerable amount of cytoplasm, in other words, to cells with a nucleus-plasma relation markedly in favor of the nucleus, but not so excessively so as to preclude the initiation of mitotic division. It may well be imagined that in such cells the centrosomes are stimulated to growth and to multiple division, instead of to the usual single division, in order to divide the mass of hypertrophied chromosomes. Two explanations are offered for the multipolar mitotic divisions in such cells: (1) that the centrosomes are incited to multiple division by some external agent, as occurs in certain egg cells as the result of the influence of various chemicals; and (2) that in the rapid growth of these anaplastic cells the centrosomes as well as the other structures grow excessively and undergo multiple instead of normal single division.

### *Amitosis* (*Primitive Mitosis*).

The rôle of amitosis as a factor in the proliferation of tumor tissue merits consideration. In such a consideration, however, one is confronted by the difficulty of determining just what constitutes direct division. Under this type of division are included simple constriction of the nucleus into two halves, nuclear fission following division of the karyosome, and even that form in which a ring-shaped attraction sphere seems to be the active agent in constricting the nucleus into two parts (salamander spermatogonia, Meves (1891)). The essential characteristic of amitosis, then, seems to be the absence of a spindle figure and of individualized chromosomes. Wilson (1897), in reviewing the literature of the subject, points out the rarity of direct division in metazoan cells and concludes that amitosis is a secondary process which indicates the beginning of the end of a series of divisions. We wish to point out the occurrence, in tumor cells, of a mode of division strikingly like amitosis, not as an argument against the correctness of the above conclusion as to the secondary nature of direct division, but as proof of the reversion by tumor cells to a very primitive form of mitosis. We believe it must be granted that such cells can and do employ biological processes which may differ from those utilized by normal tissue cells of the kind from which the tumor cells are derived. If the cell which is to give rise to a tumor could exhibit only those phenomena characteristic of its normal neighbors, it would run the same life cycle as these latter and would have the same destiny—there could be no tumor.

In the description of Tumor No. 3 we have noted the stages in a form of nuclear division in which the karyosome plays a part, without any evidence of centrosomes or spindle figure. Although the process is very much like many which have been considered amitotic divisions, we believe that the participation of the karyosome is evidence of a reversion to a primitive mitosis. While a phylogenetic seriation of the various types of karyokinesis is not possible, these types can be arranged in series by selecting species not necessarily related to each other in the scheme of evolution. Calkins (1903) has pointed out that in the most primitive form of division the division material, corresponding to the attraction sphere, is permanently intranuclear. In somewhat more complicated divisions the sphere, intranuclear in the resting nucleus, becomes extranuclear during division. And, finally, there are all the modifications in which the sphere is permanently extranuclear and often manifests itself only during mitosis. Goldschmidt and Popoff (1907) also place under karyokinesis, as its most primitive type, the division which takes place in those nuclei ("centronucleus," Boveri) in which a karyosome ("nucleolo-centrosome," Keuten, Blochmann) inaugurates the division. In such divisions individualized chromosomes may (*Euglena*) or may not (*Amoeba crystaligera,* several species of coccidia) be formed. The kind of division described in Tumor No. 3 (Plates III and IV, Figs. 24 to 30) bears a very marked resemblance to that which occurs in the protozoan nuclei above mentioned. It is met with in greatest frequency in the advancing, invading, and most rapidly growing portions of the tumor and occurs more particularly in nuclei not overladen with chromatin. It is seen in those portions of the tumor in which evidences of degeneration are least marked, and the proportion of cells which show it is so large as to indicate that it plays an important part in the proliferation of the tumor tissue. We have observed it not only in this tumor, but also in a number of others, always in those areas in which the growth is rapid and the individual cells not markedly depressed. We wish to call attention, therefore, to the frequent occurrence, in tumor cells, of a mode of division which closely simulates the direct. We prefer to think, however, that the division is a very primitive mitosis, one in which the karyokinetic center has reverted to its primordial permanent intranuclear situation, the result being a form of division which leads to a marked increase in the division rate of tumor cells.

The relationship of nuclear budding to amitosis has long been recognized. In protozoan cells it is a true reproductive process; in metazoan cells it is associated most often with functional activity. In Tumor No. 3, we have described the participation of the karyosome in single and multiple nuclear budding (Plate IV, Figs. 31 to 36). Here the process seems to be a modification of the primitive mode of mitosis discussed above. Multiple budding occurs in hyperchromatic nuclei with hypertrophied and hyperchromatic karyosomes. The multiple fission of the karyosome may, perhaps, be due to the same factors which cause the multiple division of the centrosome in multipolar mitosis.

### GIANT CELL FORMATION.

We are able to recognize three distinct types of giant cell formation in tumors: (1) separation of giant cells from syncytia; (2) plasmogamy; and (3) excessive growth of single cells.

1. *The Separation of Giant Cells from Syncytia.*—From the syncytial masses of syncytiomata—uterus, testis and Tumor No. 1—large and small cells are split off and lie free as new cells in the tissue or blood spaces. The giant cells thus produced usually possess multiple nuclei of the same type as those of the syncytial tissue.

2. *Plasmogamy.*—The fusion of tumor cells resulting in giant cell formation occurs chiefly among depressed cells in the centers of the alveoli of certain epidermoid carcinomata of slow growth, usually in those in which whorls of cells occur. The cells fuse sometimes by processes, but usually along their flattened sides, thus forming large multinucleated giant cells. The nuclei are usually hyperchromatic and often shrunken. The process is analogous to plasmogamy among depressed protozoa and in the thymus cells, in which, as Marcus (1908) has shown, the Hassall bodies are masses of fused epithelioid cells. These giant cells show various types of degeneration and most of them perish.

While the two modes of giant cell formation mentioned above are to be regarded as degenerative rather than regulatory processes, they are included here for the sake of illustration and completeness.

3. *Excessive Growth of Individual Cells.*—This is the common method of giant cell formation in tumors. Two types are to be

distinguished: (*a*) those cells in which the increase in growth is on the part of the nucleus or at least largely confined to nuclear growth, and (*b*) those in which, in addition to the nuclear growth, cytoplasmic growth is excessive.

(*a*) *Nuclear Overgrowth.*—In this first type, the single nucleus, either round, oval or lobulated (the result of budding), is usually vesicular, but often markedly hyperchromatic, and has increased greatly in size, possibly suddenly. It has stretched the original amount of cytoplasm over its increased volume, with but slight if any growth of the cytoplasm. These are really cells with markedly hypertrophied giant nuclei. They are in marked depression, from which they may, perhaps, recover by accomplishing nuclear budding (of which there is evidence) or by growth of cytoplasm to catch up with the giant nucleus.

(*b*) *Combined Cytoplasmic and Nuclear Overgrowth.*—In this type, which is the usual one, the greatly increased size of the cell is evidently due to a marked growth of the cytoplasm, following or coincident with the growth of the nucleus. Here the growth energy and capacity of the cytoplasm are great. The same growth energy would result in the production of a large number of small cells. But the cytoplasm growth is not accompanied by division energy sufficient to divide the large nucleus by mitosis, or the rates of cytoplasmic and nuclear growth, which in the normal cell bear a definite relation to each other, are so altered that there is not produced the nucleus-plasma tension necessary for division.

The increased growth energy of the cytoplasm may be accompanied by great capacity to break down nuclear material in the same manner in which nuclear hypertrophy and hyperchromatism are prevented or recovered from, that is, by chromidiosis and nuclear resorption, and in this case these processes are marked in the giant cells, as in Tumor No. 10 (Plate VI, Figs. 74, 81 and 84), and with the same results as regards recovery from depression as those described in smaller cells.

## BUDDING IN GIANT CELLS.

In many cases, however, the giant cell can neither accomplish mitosis nor inaugurate nuclear resorption and chromidiosis. The cytoplasm, however, may still possess a large control over the nucleus, for, in many instances, there occurs nuclear budding, in which, as has been shown, we have traced a primitive method of nuclear division, in consequence of which there is produced a large number of daughter nuclei, with evident reduction of nuclear hyperchromatism. And with the nuclear material thus scattered in the cytoplasm rather than gathered in a single hyperchromatic nucleus, the cell may avoid fatal depression, and may preserve its life at least as a multinucleated giant cell, though its power of further division may not be always regained. In such a cell, though the larger part of the cytoplasm may die and the mother nucleus may disintegrate, portions of the cytoplasm about vesicular budded nuclei may be quite normal (Plate V, Fig. 46). In such a cell and in multinucleated giant cells with all the cytoplasm in normal condition, the cytoplasm about some of the nuclear buds may separate off from the mother cell and give rise to two or more cells—a very primitive type of cell division, somewhat analogous to the splitting off of separate cells from syncytia.

The numerous nuclei of the multinucleated giant cell are, in our experience, always the result of nuclear budding and this is in some cases preceded by definite divisions of the karyosome of the mother nucleus (Plate IV, Figs. 34, 35 and 36), and in other cases (Plate VI, Figs. 85 and 86) it is associated with the formation of definite strands of chromatic material—perhaps a primitive type of chromosome formation.

### THE DIVISION OF BUDDED NUCLEI AND THE EXTRUSION OF NUCLEAR BUDS.

The cytoplasm of some giant cells with hyperchromatic giant nuclei may so far gain in ascendency as to destroy and extrude nuclear buds, after which there may occur mitosis of the mother nucleus (Plate V, Figs. 48, 49 and 50) or of one or more of the daughter nuclei. There are analogies for this phenomenon of mitosis after budding in other types of cells. Gurwitsch (1904) pictures the occurrence of mitosis following amitosis in the large cells of the triton blastomere. The reduction of nuclear material by the extrusion of the products of nuclear division in the maturation divisions of the egg cell is closely related in principle with the casting out of nuclear buds from the cytoplasm of tumor cells. Though in the egg cell the direct object of the maturation divisions and the extrusion of the polar bodies is to reduce the amount of chromatic material for another purpose, to make room for the chromosomes to be furnished by the spermatozoön, the result is the same in both cases, a reduction of the chromatin content of the nucleus to a degree compatible with the normal destiny of each of these two varieties of cell—as shown, partly at least, by their inherent tendency to multiple repeated divisions.

It is in tumors whose division rate is very rapid or at least moderately rapid that these various nuclear reduction phenomena associated with marked growth capacity of the cytoplasm occur. The nuclei of the giant cells in slowly growing tumors—giant-cell sarcomata of the usual type, for instance—often bud and the cytoplasm may gradually grow to a very considerable size, but so far as our observation goes, the cytoplasm does not break down or extrude nuclear buds and the mother nucleus after the budding process does not divide by mitosis. These phenomena are accomplished apparently only in moderately rapidly and in rapidly growing tumors, in whose cells the cytoplasm has not only great growth capacity, but the property of disposing of nuclear material.

## KARYOGAMY.

It has been pointed out above that tumor cells may employ all the regulatory processes utilized by tissue, sex and protozoan cells, except the phenomenon of karyogamy, a regulatory process to which, in the form of conjugation, copulation or autogamy, protozoa and sex cells finally resort as their last defense against fatal depression.

None of the appearances hitherto described as indicative of karyogamy—the copulation phenomena of Farmer, Moore and Walker (1906) and the conjugation of Bashford (1904)—withstand critical analysis and no adequate series of morphological appearances has been brought forward to support the claims made in this regard. The mere presence of leukocytes within tumor cells is far from being convincing evidence of copulation to those who are acquainted, on the one hand, with the invasive habits of these cells and the ingestive capacity of protozoan and metazoan cells and, on the other hand, with the phenomena of the various steps and types of the fertilization process. The establishment of the occurrence of heterotypical mitosis in tumor cells would not be of necessity evidence of either copulation in or of the gametoid nature of these cells, for, as Marcus (1908) has shown in his work on the thymus cells, heterotypical mitosis is simply evidence of nuclear hyperchromatism. The appearances described by Bashford (1904) as tumor cell conjugation appear to us to be stages in nuclear budding. Compare, in this regard, our Fig. 87 (Plate VI) with Fig. 32 of Bashford's article. At the present time, it is on theoretical grounds alone that karyogamy in tumor cells has any substantial footing.

The tumor cell is the only known cell capable of indefinite proliferation without fertilization. This or some compensating process must occur in the cells of certain tumors, such as the Jensen tumor, which appear capable of indefinite proliferation. The type of fertilization most likely to occur in such cells would be the autogamous.

## V. CONCLUSIONS.

Departure from the simple alveolar structure of protoplasm (morphological differentiation) is an expression of functional specialization.

Nucleus and cytoplasm are mutually interdependent.

For every normal cell there is a definite relation between the amount of cytoplasm and the nuclear mass—the nucleus-plasma relation.

The rates of cytoplasm growth and nucleus growth vary. The maximum disproportion between the two, in the normal cell, leads to a condition of nucleus-plasma tension, which inaugurates rapid divisional growth of the nucleus and results finally in cell division.

Many conditions, among them overfeeding, starvation, hyperactivity, changes in temperature, rapidly repeated divisions, lead to an upset of the nucleus-plasma relation, characterized by nuclear hypertrophy and hyperchromatism, and often nuclear hyperplasia.

Excessive chromatin consumption due to excessive functional activity and, in tumor cells, to an increase in the property of cytoplasm to disintegrate nuclear material, leads to an upset of the nucleus-plasma relation in favor of the cytoplasm, which may cause physiological degeneration and death.

The previously described regulatory processes by means of which cells, other than tumor cells, avoid and recover from depression are: (1) growth of cytoplasm with differentiation and functional activity; (2) cell division; (3) nuclear resorption and chromidiosis, often followed by cell division; (4) dissolution and extrusion of nuclei; (5) the renewal of chromatin during rest; and (6) karyogamy.

Dynamic energy, produced by cellular metabolism, manifests itself in cellular growth and function. The amount of energy production of which cells are capable varies for the different species of cells and, within limits, for cells of the same species. In all normal cells energy production becomes exhausted unless there is provided a rejuvenation of protoplasm and a restoration of its potentiality for the production of energy by some form of fertilization. This exhaustion is manifested by senility, physiological degeneration and death of the cell.

In the malignant tumor cell the maximum limit of energy production for the normal cell is overstepped and the energy produced is abnormally distributed to the advantage of growth rather than of function.

The increased growth rate of tumor cells leads to an increased division rate.

Rapidity of growth is usually accompanied by lack of differentiation. But the loss of differentiation may be so complete that individual cells with a fixed division rate are not produced. Such complete anaplasia might be followed, if an accession of growth energy becomes possible, by metaplasia and the production of mixed tumors.

The rapid division rate of tumor cells is followed, as in protozoan, sex and thymus cells, by depression.

Excessive nuclear hypertrophy leads to the formation of giant cells, in which the increased size of the cell may be due largely to nuclear growth alone. In other cells nuclear growth is associated with cytoplasmic growth. In such cells attempts at regulation may be active. Nuclear budding is the usual method and leads to the production of multinucleated cells. Giant cells in tumors, in addition to being produced by growth of single cells, may be formed by the splitting off of multinucleated masses from syncytia and by plasmogamy (fusion). Giant cells produced by the two latter processes fall into depression and undergo physiological degeneration and death.

To avoid and overcome depression, tumor cells employ all the regulatory processes used by other cells except, so far as we now know, karyogamy.

In addition to these, we have pointed out the occurrence of nuclear budding and its purposeful nature in reducing superabundant nuclear material, following which cell division may occur with or without mitosis.

After nuclear hyperchromatism has been reduced by budding, buds may be extruded, and there may occur mitosis in the mother nucleus or in some of the buds. Or again, cell division may occur with the separation of masses of cytoplasm about nuclear buds.

We believe that the dropping of chromosomes from hyperchromatic mitoses, and the reversion to a very primitive type of mitosis, are also to be regarded as regulatory mechanisms.

It is evident from our observations that amitosis and primitive mitosis are responsible for much of the cell multiplication in tumors.

Whether the growth rate of any given malignant tumor is slow, moderately rapid or rapid depends upon the growth and divisional capacities of the species of normal cell from which the tumor cells were derived, the strength of the incitants which stimulate growth and division, and the degree to which active regulatory processes are developed and utilized by the cells. The growth rate of a given tumor may be varied by the development of modes of regulation not before used by that tumor.

The utilization of the regulatory mechanisms, which have been mentioned above, helps to explain a large degree of the apparently unlimited proliferative capacity which is so characteristic of the cells of malignant tumors.

Theoretically, the unlimited proliferation of which the cells of certain malignant tumors seem capable demands the occurrence of some form of karyogamy as the ultimate means for overcoming what must otherwise be a fatal depression. The evidence thus far adduced in favor of copulation and conjugation in tumor cells is not, however, satisfactory.

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## EXPLANATION OF PLATES.

All drawings were made with the Spencer camera lucida. In their preparation, except in the case of Fig. 1, two lens systems were used giving, respectively, magnifications of 1,395 and 1,480 diameters.

### PLATE I.

FIGS. 1 to 4. Tumor No. 1. Epulis of lower jaw. Mayer's acid hemalum and eosin. FIG. 1, Leitz 7 objective, Zeiss 6 compensating ocular; × 990. FIGS. 2, 3 and 4, Zeiss 2 mm. objective, 6 compensating ocular; × 1,480. In the reproduction Figs. 1, 3, and 4 have been reduced by $\frac{1}{3}$, and Fig. 2 has been reduced by $\frac{5}{12}$.

FIG. 1. Syncytial tissue composing the greater portion of the section. The tissue shows numerous wide blood spaces which do not have an endothelial lining.

FIG. 2. Syncytial tissue. Formation of spaces in the protoplasm. Some spaces contain red blood corpuscles. About some of the nuclei the cytoplasm has become differentiated with the formation of individual cells.

FIG. 3. A multinucleated giant cell, surrounded by blood spaces. The formation of such cells seems to be determined by the blood spaces. A few mononucleated cells have also been produced in the same way.

FIG. 4. Two multinucleated giant cells showing beginning degeneration. The cytoplasm is somewhat vacuolated in places and some areas take the hematoxylin stain. The nuclei are decreased in size, several are irregular in outline and all stain deeply and show little structural detail.

FIGS. 5–10. Tumor No. 2. Carcinoma of the mucous membrane of the cheek. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Leitz $\frac{1}{12}$ objective, 4 ocular; × 1,395.

FIG. 5. A cell with an hypertrophied, hyperchromatic nucleus.

FIG. 6. A cell with an hypertrophied budding nucleus.

### PLATE II.

FIG. 7. A cell with a giant, budding, hyperchromatic nucleus.

FIG. 8. A cell with a giant, hyperchromatic nucleus and vacuolated cytoplasm.

FIG. 9. A cell with a giant, hyperchromatic nucleus showing condensation and vacuolization of the nuclear material; disintegration of the cytoplasm at one side.

FIG. 10. A giant cell with marked vacuolization of the cytoplasm; the large nucleus contains one large and numerous small masses of vacuolated nuclear material.

FIGS. 11–36. Tumor No. 3. Giant cell sarcoma of the esophagus. Heidenhain's iron hematoxylin and eosin. Zeiss 2 mm. objective, 6 compensating ocular; × 1,480.

FIG. 11. The majority of the cells in the older portions of the tumor are of this type.

FIG. 12. Budding, I: a giant nucleus so hyperchromatic that the reticulum is completely hidden. Early amitosis-like division with several early small buds.

FIG. 13. Budding, II: two buds are almost completely separated. The structure of the original nucleus is much like that of Fig. 11. The buds are less hyperchromatic.

## PLATE III.

FIG. 14. Budding, III: the process still further advanced than in Fig. 13. There are numerous buds, the hyperchromatism of which and of the original nucleus is greatly reduced.

FIG. 15. Budding, IV: end stage. Formation of separate daughter nuclei of a very primitive type. The nuclei are rich in fluid, with a distinct membrane and widely meshed reticulum. The chromatin is small in amount and confined to the karyosome. Several of the nuclei (at *a, b, c*) show beginning degenerative changes—decrease in size, shrivelling of the membrane and condensation of the nuclear fluid.

FIG. 16. A type cell from the advancing border of the tumor.

FIGS. 17 and 18. Stages in the normal process of chromatin deposition in the karyosome, leading to the formation of a cell like Fig. 16.

FIGS. 19 and 20. Plastin hypertrophy of the karyosome.

FIG. 19. An hypertrophied, vacuolated, chromatin-free karyosome.

FIG. 20. A nucleus with three hypertrophied, chromatin-free karyosomes.

FIGS. 21, 22 and 23. Stages in nuclear hyperchromatism.

FIG. 21. An hypertrophied, hyperchromatic karyosome.

FIG. 22. Beginning chromatin diffusion throughout the nucleus.

FIG. 23. Marked chromatin diffusion throughout the nucleus; the nucleus is so hyperchromatic that the reticulum can not be seen.

FIGS. 24–29. Stages in the equal binary fission of the karyosome, leading to nuclear division.

## PLATE IV.

FIG. 30. Stage in the equal binary fission of the karysome, leading to nuclear division.

FIGS. 31–33. Stages in the unequal binary fission of the karyosome, leading to single nuclear budding.

FIGS. 34–36. Stages in the multiple fission of the karyosome, leading to multiple nuclear budding.

FIGS. 37–50. Tumor No. 4. Epithelioma of the cervix uteri. Mayer's acid hemalum and eosin. Zeiss 2 mm. objective, 6 compensating ocular; × 1,480.

FIG. 37. A type cell.

FIG. 38. A cell with an hypertrophied, hyperchromatic nucleus.

FIG. 39. A giant cell in abortive mitosis, showing degeneration of the hypertrophied chromosomes.

FIG. 40. A cell whose hypertrophied nucleus has just undergone amitosis.

FIGS. 41 and 42. Giant cells showing stages of nuclear budding.

FIG. 43. A giant cell in which budding has produced many nuclei. The cytoplasm shows vacuolar and hyalin degeneration.

Fig. 44. A cell with two nuclei. One is completely vacuolated and surrounded by hyalin cytoplasm; the other is less completely degenerated and surrounded by vacuolar cytoplasm.

## Plate V.

Fig. 45. A giant cell dead of depression.

Fig. 46. A very large giant cell. Most of the cytoplasm is hyalin, and the mother nucleus is degenerated and broken into fragments. Four nuclear buds are surrounded by well preserved cytoplasm.

Fig. 47. A small cell dead of depression.

Fig. 48. A large cell showing three nuclear buds and a portion of a mitotic figure in cross section.

Fig. 49. A large cell with a cross section of a mitotic figure, and a chain of degenerated nuclear buds at one side.

Fig. 50. A cell showing a mitotic figure in longitudinal section, and a mass of degenerated nuclear buds extruded from one pole of the cell.

Figs. 51–54. Tumor No. 5. Hypernephroma. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Leitz $\frac{1}{12}$ objective, 4 ocular; × 1,395.

Fig. 51. A cell with a small extranuclear chromatin granule and a pigment granule.

Fig. 52. Cells showing marked pigmentation; the nuclei are vesicular and not hyperchromatic.

Fig. 53. A cell with a large amount of pigment; the nucleus is very small and poor in chromatin.

Fig. 54. A cell showing extreme pigmentation; no nuclear material can be seen.

Figs. 55–59. Tumor No. 6. Carcinoma of the thyroid. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Leitz $\frac{1}{12}$ objective, 4 ocular; × 1,395.

Fig. 55. From the peripheral portion of the recurrence. Cells from the wall of an acinus. The cytoplasm is markedly vacuolated. (*a*) A cell with a well-regulated nucleus. (*b*) A cell with an hyperchromatic nucleus, whose membrane is shrunken. (c) Chromidiosis with beginning reconstruction of the nucleus.

Fig. 56. From the cervical lymph gland invasion. (*a*) and (*b*) Type cells. (*c*) A cell with a giant nucleus.

Fig. 57. Small cells with very hyperchromatic nuclei.

Fig. 58. From the lung metastasis. Chromidiosis; almost all the chromatin has left the nucleus.

Fig. 59. From a lung metastasis. Mitosis. (*a*) Bouquet stage; two chromatin rods not incorporated in the figure. (*b*) Equatorial plate; two chromatin particles have not been drawn into the plate.

Figs. 60–63. Tumor No. 8. Carcinoma of the breast. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Zeiss 2 mm. objective, 6 compensating ocular; × 1,480.

Fig. 60. From the metastasis. Two resting cells which are reducing their chromatic material by chromidiosis.

Fig. 61. From the metastasis. A cell showing partial dissolution of its nucleus into chromidia.

910. 24

Fig. 62. From the metastasis. (*a*) A resting cell showing chromidiosis. (*b*) A dividing cell in the bouquet stage, showing chromidiosis.

Fig. 63. A cell whose nucleus has been completely transformed into chromidia.

Figs. 64–70. Tumor No. 9. Carcinoma of the lung. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Leitz $\frac{1}{12}$ objective, 4 ocular; × 1,395.

Fig. 64. From a liver metastasis. A type cell.

Fig. 65. From an omental metastasis. Markedly hyperchromatic nuclei with chromidiosis.

Fig. 66. From an intestinal metastasis. A cell with a markedly hyperchromatic giant nucleus.

Fig. 67. From an intestinal metastasis. Nuclear hypertrophy and hyperchromatism.

Fig. 68. From an omental metastasis. Marked chromidiosis, with a return of the nucleus to the vesicular type.

## PLATE VI.

Fig. 69. From an omental metastasis. Marked chromidiosis. Breaking up of the hyperchromatic nucleus.

Fig. 70. From an intestinal metastasis. Vacuolization of an hyperchromatic nucleus.

Figs. 71–86. Tumor No. 10. Giant cell sarcoma of the neck. Grenacher's alcoholic borax-carmin and dilute Delafield's hematoxylin. Zeiss 2 mm. objective, 6 compensating ocular; × 1,480.

Fig. 71. A type cell. The cytoplasm is closely meshed. The nucleus is rather vesicular, with a fine reticulum and small chromatin granules lying within the nucleus and upon the inner surface of the membrane.

Fig. 72. Very moderate hyperchromatism leading to the formation of a vesicular nucleus with several large chromatin masses.

Fig. 73. Marked hyperchromatism and giant nucleus formation.

Fig. 74. An hyperchromatic nucleus which shows the beginning of chromatin extrusion.

Fig. 75. Marked chromidiosis in a small hyperchromatic nucleus.

Fig. 76. A cell showing some finely granular, extranuclear chromatin and a considerable amount of finely granular, faint brown pigment scattered in the cytoplasm. Chromidiosis has resulted in the production of a vesicular nucleus.

Fig. 77. A peculiar type of cell, present in considerable numbers. The nucleus is small, round, dense and hyperchromatic. The cytoplasm is vacuolated.

Fig. 78. Chromidiosis in a nucleus of the type shown in Fig. 77.

Fig. 79. Resorption, without destruction of the membrane, in a nucleus of the type shown in Fig. 72. In places the cytoplasm takes a faint chromatin stain.

Fig. 80. Partial resorption of a nucleus of the type shown in Fig. 77.

Fig. 81. Nuclear resorption in a nucleus of the type shown in Fig. 74. The nuclear membrane, at one side, has disappeared.

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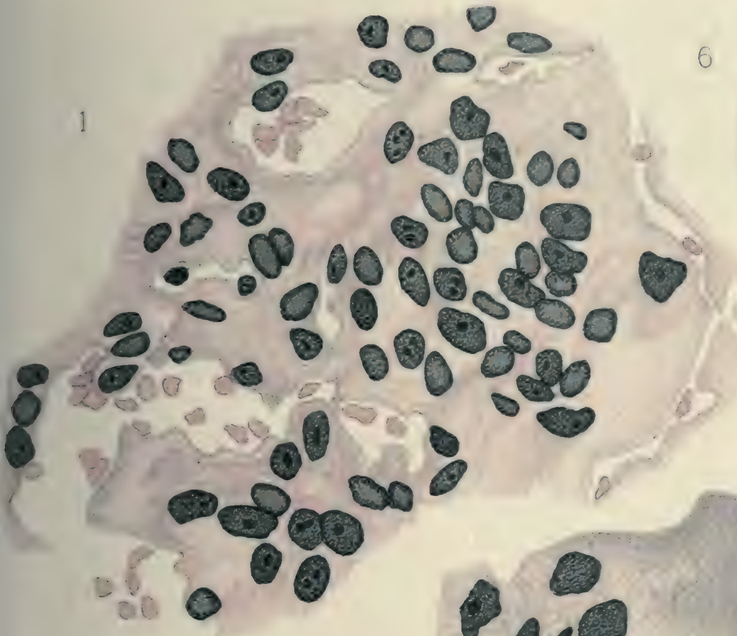

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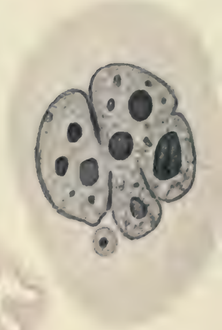

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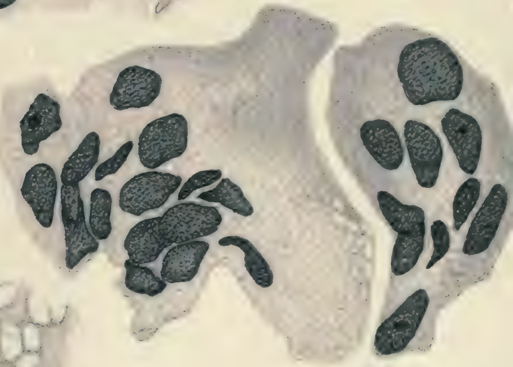

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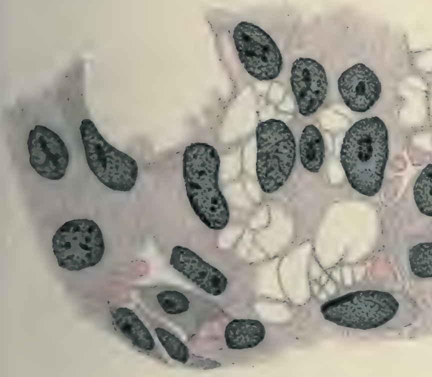

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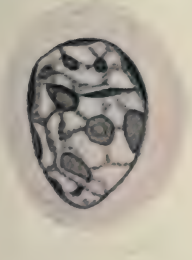

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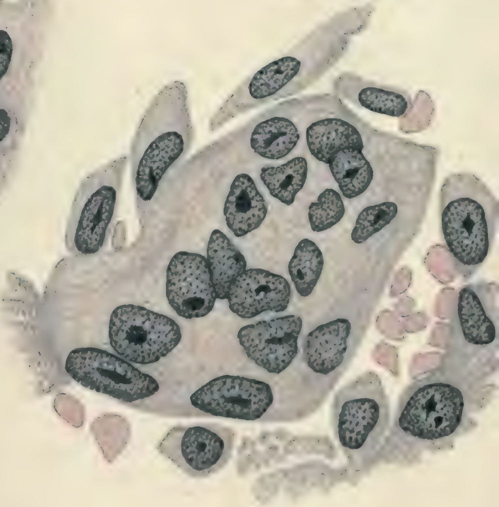

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MONOGRAPH NO. 2. PLATE II.

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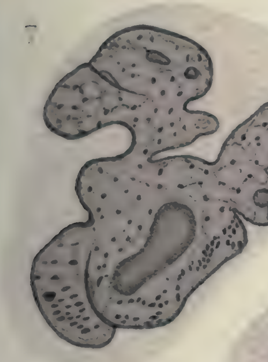

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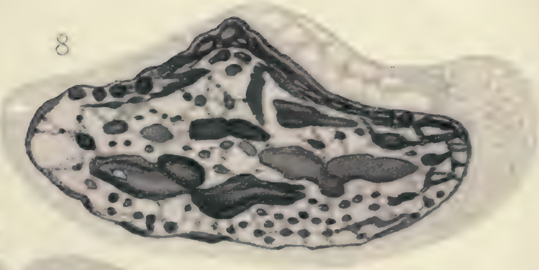

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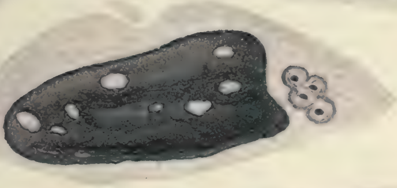

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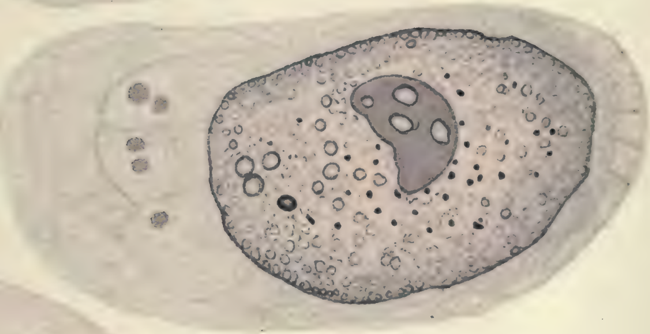

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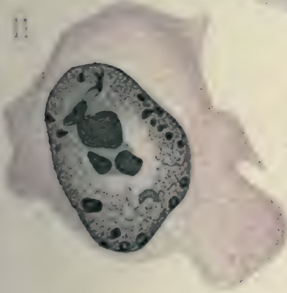

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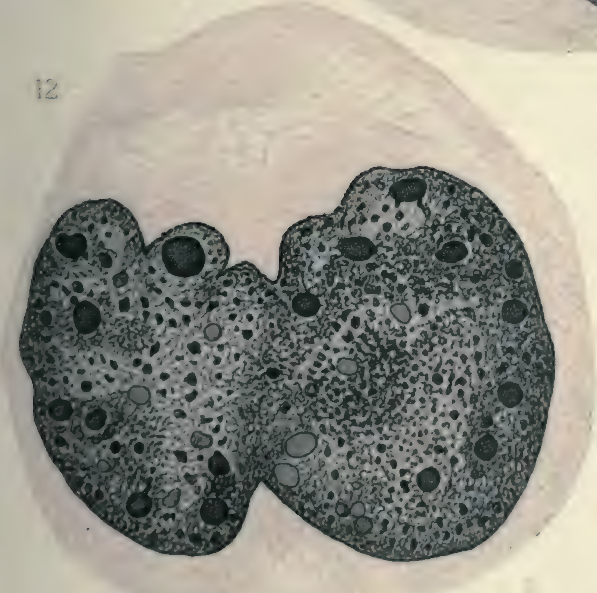

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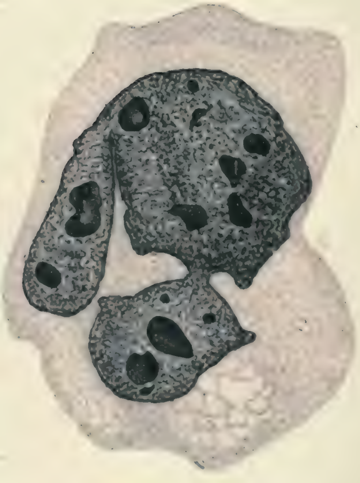

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MONOGRAPH NO. 2.

PLATE III.

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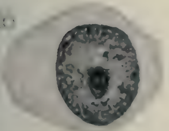

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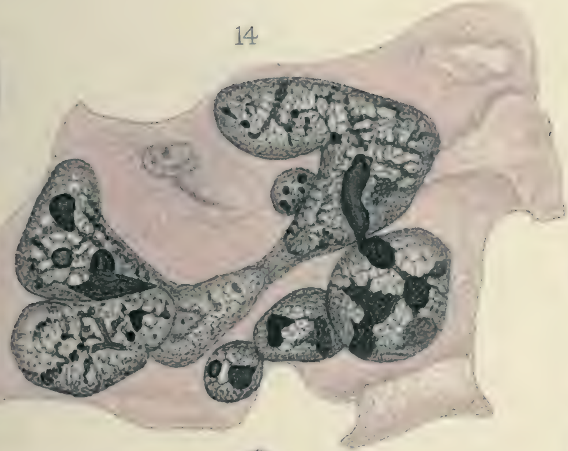

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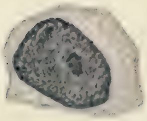

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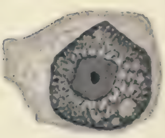

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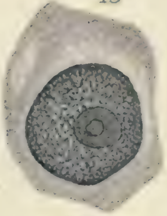

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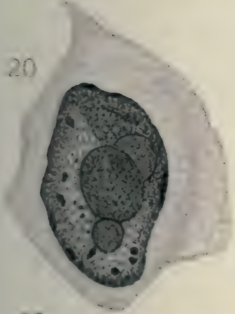

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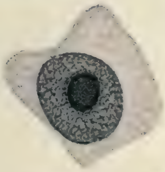

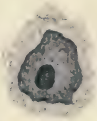

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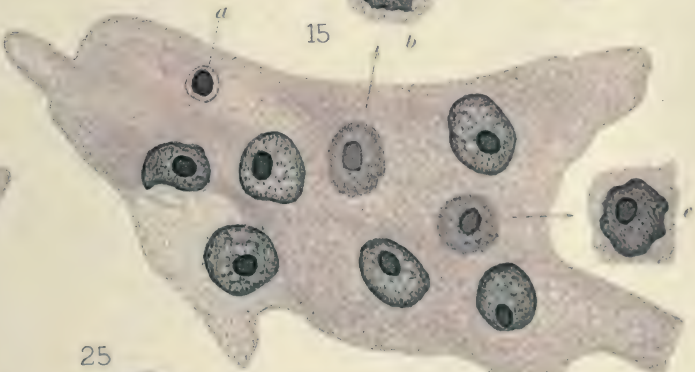

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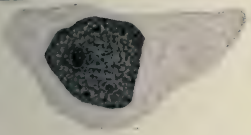

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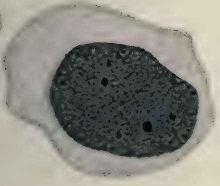

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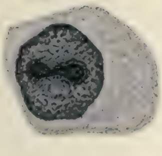

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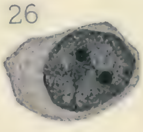

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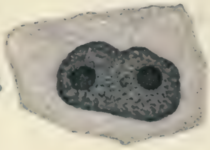

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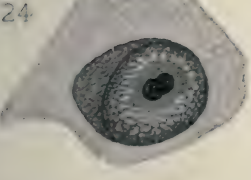

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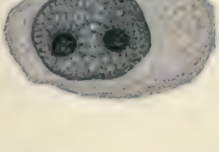

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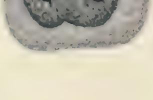

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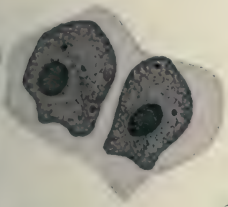

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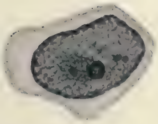

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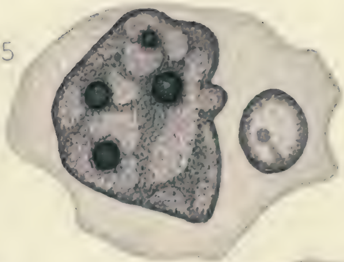

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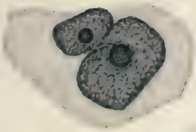

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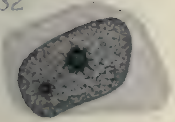

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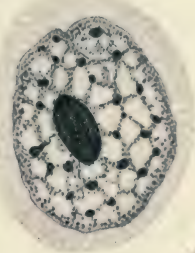

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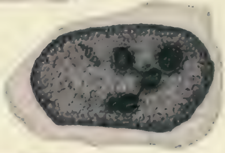

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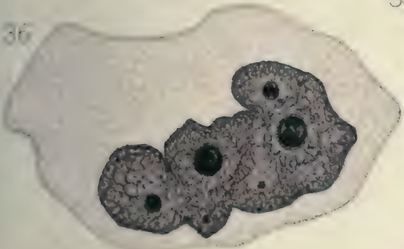

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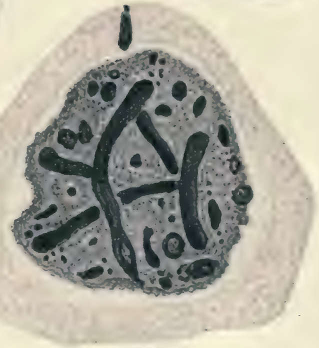

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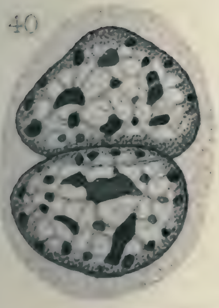

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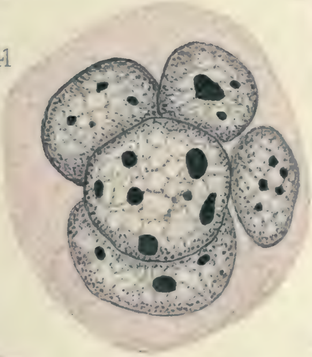

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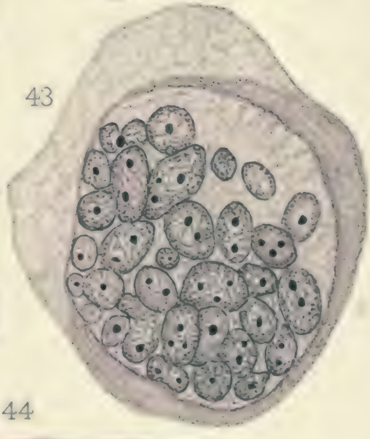

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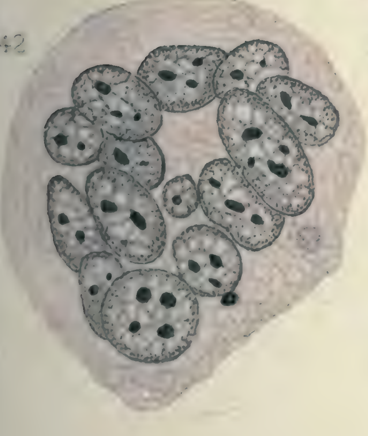

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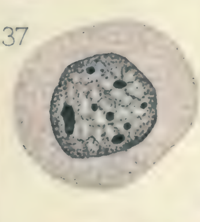

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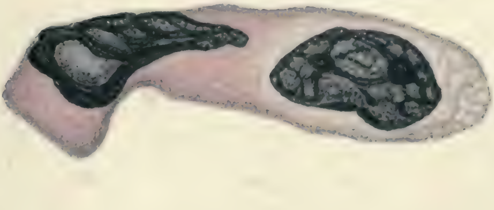

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MONOGRAPH NO. 2. PLATE V.

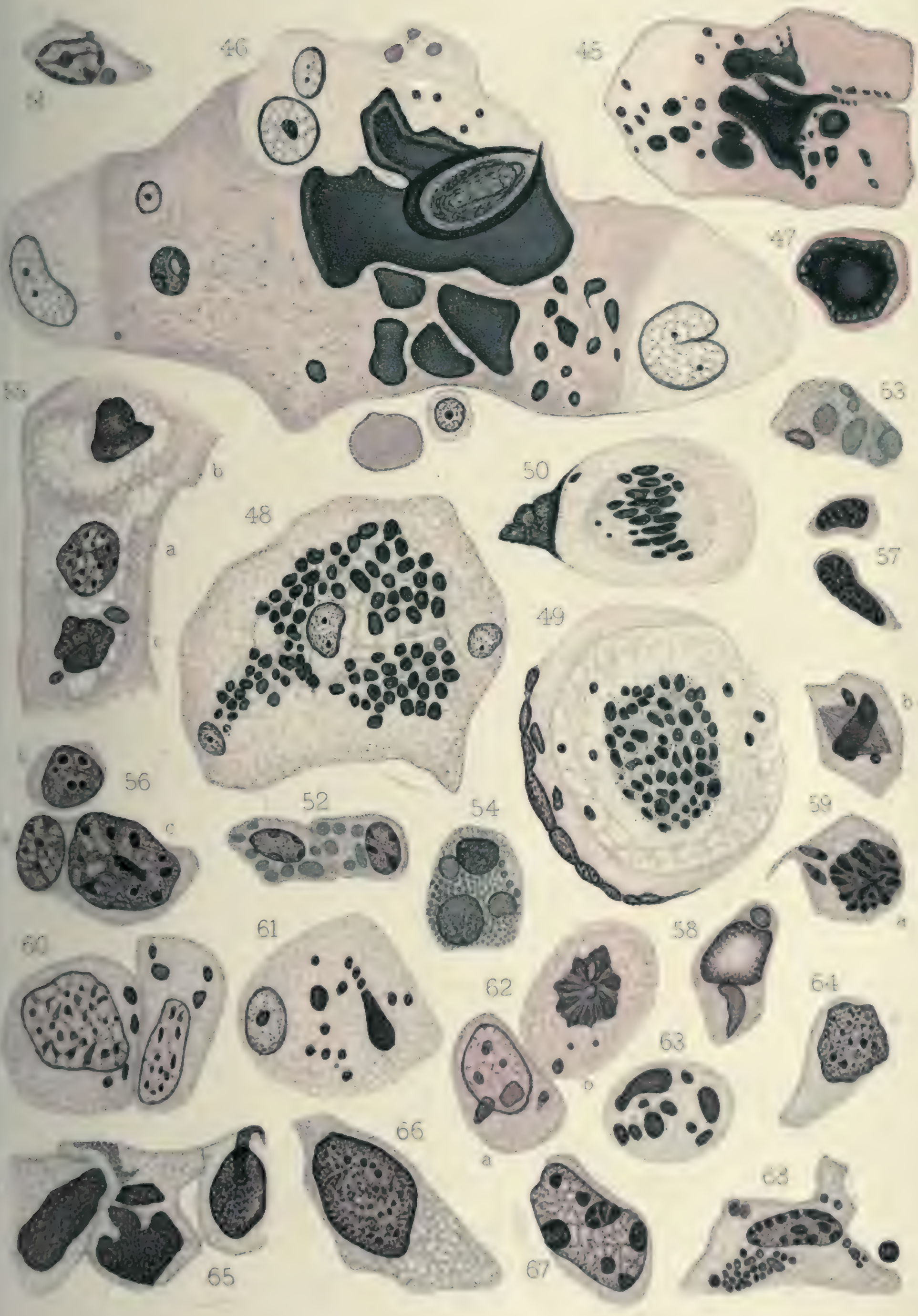

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PLATE VI.

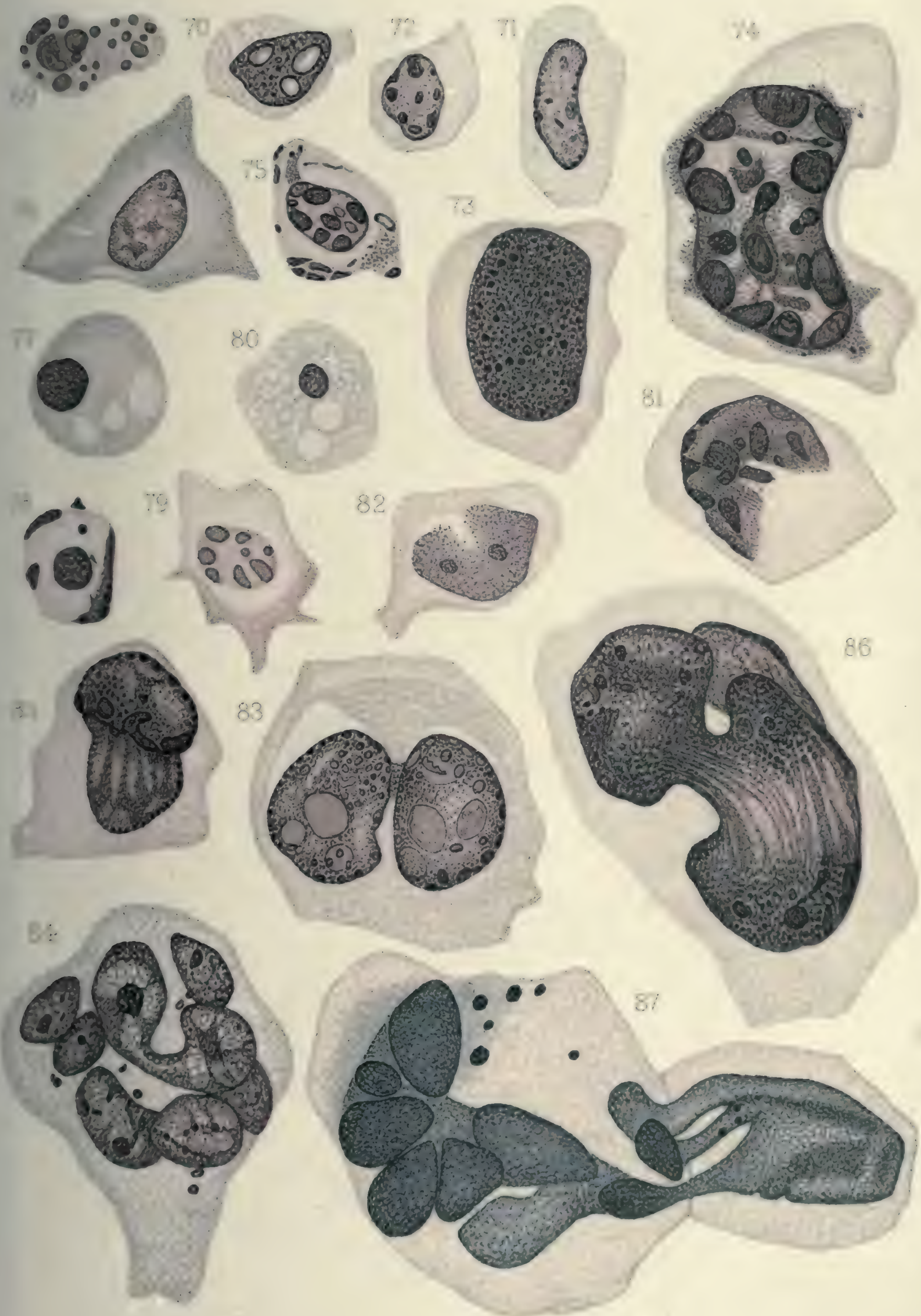

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Fig. 82. Partial resorption of a nucleus of the type shown in Fig. 73. Disappearance of the membrane at one side.

Fig. 83. Amitosis. The division has resulted in the production of two nuclei which are only slightly hyperchromatic.

Fig. 84. Budding and chromidiosis. The nuclear buds are vesicular.

Figs. 85 and 86. Nuclear changes due, apparently, to a sudden increase in the amount of the fluid contents of the nuclei, resulting in the production, within the nuclei, of chromosome-like strands.

Fig. 87. From the axillary lymph gland metastasis of a carcinoma of the breast. Delafield's hematoxylin and eosin. Zeiss 2 mm. objective, 6 compensating ocular; × 1,480. A cell showing chromidiosis, nuclear budding and beginning cytoplasmic division.

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Figs. 5–10, 37–50, and 60–63 by William Travis Howard.

Figs. 1–4, 11–36, 51–59, and 64–87 by Oscar T. Schultz.

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No. 25.

# The Rôle of Nuclear Budding in the Regulation of Tumor Cells.

By

William Travis Howard,
Cleveland, Ohio.

(From the Pathological Laboratories of Western Reserve University
and of the Lakeside Hospital, Cleveland, Ohio.)

With Plates 1—3.

# Introduction.

Thanks to the investigations of MAUPAS, CALKINS, RICHARD HERTWIG and the latter's pupils, it is now well established, that certain protozoa, after cultivation for a long time and through many generations, cease to multiply, fall into depression or physiological degeneration, and finally die. The complete degeneration leading to death is preceded by alternate periods of depression and recovery with active multiplication.

These facts have been worked out in a thorough manner on Paramaecium, Dileptus gigas, Frontonia and Stylonychia by R. HERTWIG (1900) and by POPOFF (1907 b) and on Actinosphaerium Eichhorni by R. HERTWIG (1904) and by HOWARD (1908).

R. HERTWIG (1900, 1904) has attributed this depression to the marked increase in the amount of the nuclear material in proportion to the cytoplasm; that is, to an upset of the nucleus plasma relation in favor of the nucleus.

A similar depression, characterized especially by a marked upset of the nucleus plasma relation, has been noted by R. HERTWIG (1903) and by POPOFF (1907 a) in certain sex cells and by MARCUS (1908) in the cells of the rapidly growing thymus during the development of this organ. One of the most important additions to our knowledge of the cell that has arisen from these studies is R. HERTWIG's nucleus plasma relation theory and his conception of the rôle of the nucleus plasma balance in the avoidance of depression and in the regulation of the cell.

R. HERTWIG (1900, 1903, 1904) has shown that during the periods of recovery from depression the nuclear hypertrophy, hyperplasia and hyperchromatism so characteristic of the depression state may be reduced or even overcome by the elimination and destruction of the excessive nuclear material. The chief means by which this is accomplished are dissolution, resorption and extrusion of nuclei, nuclear fusion and chromidiosis. Coincidental with these phenomena the normal nucleus plasma relation is more or less perfectly restored and the degenerative changes of nucleus and cytoplasm so commonly present in depression may also disappear. Since cell division and fertilization may lead to reorganization of the nucleus and growth of the cytoplasm R. HERTWIG includes these phenomena among the regulatory processes of cells.

In summation it may be stated that there is convincing evidence that: 1) in rapid growth the nuclear material tends to increase at a greater rate than the cytoplasm, thus producing a nucleus plasma relation markedly in favor of the nucleus which, if not restored to normal proportions, results in depression and death of the cell; 2) cell regulation embraces all the phenomena, such as functional activity, division, fertilization, growth of cytoplasm, chromidiosis and nuclear destruction and extrusion, by means of which the nucleus plasma balance is corrected and maintained.

Tumors present an excellent material for the study of the growth and regulatory phenomena of cells. In our monograph (Studies in the Biology of Tumor Cells) Dr. O. T. SCHULTZ and I (1910) have shown, among other things, that tumor cells may and commonly do show all the phenomena of depression (hypertrophy, hyperplasia and hyperchromatism of nuclei and various degenerations of the cytoplasm) and of regulation (except fertilization) which have been described in protozoa, sex and thymus cells; that slow growth and arrest of growth are often due to depression; that rapid growth is attended by evidences of cell regulation; and that the rapidity of growth attained by a given tumor depends ultimately upon the degree of regulation attained by its cells. In different tumors and in different parts of the same tumor, different types of regulatory phenomena may be in evidence. Depression is, as a rule, most marked in the older portions of tumors. We have found that R. HERTWIG's conception that division is a phenomenon of regulation in growing cells applies to tumor cells as well as to protozoa and sex cells.

While mitosis plays a large part in the cell multiplication of tumors, amitotic division is often much more frequent and, in certain tumors, is the chief or even the only type of cell division. In some rapidly growing tumors mitosis and amitosis may occur in the same areas in cells lying near together, and, as will appear later, in the same cell.

We described two types of amitosis.

a) Binary fission or division of the nucleus into two equal or nearly equal parts.

b) Nuclear budding, in which one or more buds are thrown off from the nucleus. In the case of multiple buds, they may be thrown off simultaneously or in series.

In either binary fission or in budding of the nucleus, the division process may be inaugurated by definite binary or by multiple division of the karyosome, accordingly as the nucleus divides into two or more parts. This separation of the karyosome into two or more masses and thus inaugurating the division process is so striking and can be followed so definitely that we called the process primitive mitosis and compared it with the type of division occurring in Euglena, Amoeba crystalligera and certain species of coccidia. We suggested that as this type of primitive mitosis occurs in rapidly growing parts of tumors, the karyokinetic centre has reverted to its primordial permanent intranuclear position in these cells, resulting in a form of division leading to a marked increase in the division rate of the tumor cells.

## Material.

The description of nuclear budding given in the present paper is based upon a careful and detailed study of sections from our large collection of tumors, eleven of which are described in detail in the monograph on the Biology of Tumor Cells by Dr. SCHULTZ and myself (1910).

The fixing agents used were saturated solution of sublimate, with or without the addition of formalin, ZENKER's fluid, FLEMMING's fluid, and 10 % formalin solution.

Only well fixed material was used for study and great care was taken to avoid artefacts. The use of graded alcohols in preservation, hydration and dehydration was scrupulously adhered to. Most of our material was obtained at operation and was placed in the fixing fluids within a short time after removal from the body. The stains used were borax carmine, sometimes followed by DELAFIELD's haematoxylin with or without eosine, or HEIDENHAIN's iron haematoxylin followed in some instances with eosine.

The drawings illustrating the present paper were made from cells of tumors Nos. IV and XI of the monograph above refered to. In both cases the material was obtained at operation and placed immediately into the fixing fluids. In case IV, ZENKER's fluid and in case XI, FLEMMING's fluid and saturated sublimate solution, both with and without the addition of formalin, were used. Case IV is an example of a moderately rapidly growing squamous cell carcinoma of the Cervix uteri, and case XI one of a rapidly growing glandular carcinoma mammae. The same phenomena of amitosis described in these two tumors are equally well exemplified in various sarcomata and other carcinomata in our collection.

## Nuclear Budding.

### a) Conditions under which Budding of Nuclei occurs.

While amitosis in the two forms previously indicated occurs not infrequently in tumors of slow growth, it is much more common in those of moderately rapid and of rapid growth. Whether the earliest cell divisions in a beginning tumor are inaugurated by mitotic or by amitotic nuclear division is not known. It has been very generally assumed that they are mitotic. In the earliest of the rapidly growing tumors studied by Dr. SCHULTZ and myself, amitosis as well as mitosis was observed. Binary fission or nuclear budding may be met with in the same areas of a given tumor and often occur in cells lying side by side.

In our experience, nuclear budding in tumor cells occurs usually if not always in depressed cells. In slow growing tumors, nuclear budding is nearly always confined to giant cells and in more rapidly growing tumors it occurs, as a rule, only in cells at least twice as large as the type cell and is much more frequent in cells which are classed as giant cells. Judging from our material, it may be stated that nuclear budding is limited to cells with hypertrophied, hyperchromatic nuclei, with the nucleus plasma relation markedly in favor of the nucleus. The chain of events leading to the condition or state of the tumor cell most favorable for nuclear budding appear to be as follows. In moderately rapid as well as in rapid growth of tumor tissue, the nuclear material tends to outgrow the cytoplasm of the cells, resulting in a nucleus plasma relation in favor of the nucleus. This results, after repeated cell divisions, which are usually rapid, in the production of a number of cells smaller than the type cell and each with a relatively large hyperchromatic nucleus.

The mode of nuclear division occurring in the cell divisions leading to cells of this type may be mitotic or amitotic (binary fission) but they are probably more often mitotic. When tumor cells reach such a state of depression, several processes are open to them. They may remain alive in a state of rest without attempting division, perish from fatal depression, become regulated more or less completely by chromidiosis, nuclear resorption, or growth of cytoplasm, or division may be attempted with or without the occurrence of some of these regulatory phenomena.

Mitoses starting in such cells may abort, or multipolar mitoses may result; or chromosomes, if the division process reach this stage, may drop from the figure and lie without the spindle; or, again, some or all of the chromosomes may degenerate and break up and the cell perish. Chromodiosis previous to division in such cells may be followed by more or less normal mitosis. In some depressed cells growth of cytoplasm, often to the extent of producing giant cells, may serve to restore a normal nucleus plasma relation. Such giant cells comparatively rarely divide by mitosis. In cells which perish from depression, the excessive amount of chromatic material becomes diffused throughout the nucleus, obscuring the nuclear frame work and the nuclear membrane; the cytoplasm loses its characteristic structure and becomes hyaline (fig. 3). The nucleus may become vacuolated or break up into larger or smaller deeply chromatic fragments (fig. 4).

A correct understanding of the above processes can be gained best, perhaps, by a study of individual cells. Taking fig. 1 as a type cell, with a well balanced nucleus plasma relation, fig. 2 represents a cell in an early stage of depression, with a hypertrophied, hyperchromatic nucleus, a relatively small amount of cytoplasm and a nucleus plasma relation markedly in favor of the nucleus. Should the cytoplasm of such a cell as fig. 2 grow to such a degree as to restore the nucleus plasma relation to the normal, the result would be a well regulated giant cell, and this is not of uncommon occurrence in our tumor material. Such cells may, but rarely do, undergo mitosis. However, the nucleus may grow at the same rate as, or at a greater or somewhat slower rate than the cytoplasm and the result is a giant cell with a hypertrophied, hyperchromatic nucleus, and such cells often die in fatal depression. Again, in a cell of the type of fig. 2 chromidiosis or nuclear resorption may take place and, the nucleus plasma relation approaching the normal proportions, perfect or imperfect mitosis may result. Or, in the absence of such regulatory phenomena, mitosis may start and pathological mitosis, as above indicated, occur. Again, in cells with a nucleus plasma relation such as is present in fig. 2 amitosis by binary fission of the nucleus into two equal or nearly equal halves (fig. 5) and leading to cell division may take place and a fresh opportunity thus be given for cell reorganization. Such a cell may on the other hand pass into a resting or vegetative state and remain inactive.

Lastly, there may occur the phenomenon which is the special theme of this communication, namely, amitosis by nuclear budding. While nuclear budding may take place in cells of the relative size of figs. 2 and 5, it is usually confined to cells from two to many times the size of these, that is, to cells usually described as giant cells. The nucleus of such a cell is correspondingly large and hyperchromatic (fig. 6). In such cells normal mitosis seems to be practically impossible, and recognizable attempts at mitosis, or even amitosis by binary fission, are not common.

While binary fission of the nucleus is more commonly met with in cells two or three times the size of the type cell — in giant cells of the smaller type — nuclear budding occurs most frequently in giant cells of the larger type. Nuclear budding in tumor cells, so far as our experience goes, is not usually seen in cells which form chromidia or which practice nuclear resorption.

Nuclear budding is apparently a last resort on the part of depressed cells to regulate themselves by division and it is the only type of division possible to such cells.

## b) Varieties of Nuclear Budding met with in Tumor Cells.

We are able to recognize three types or varieties of nuclear budding in tumor cells.

In the first and simplest type one or more small buds spring from one pole of the nucleus (figs. 6 and 10). In some cases the nucleus sends off buds from both poles. Karyosomic division previous to budding has not been observed in this type. The buds first appear as small globular protuberances from the body of the nucleus projecting into the cytoplasm. They are covered with a well defined nuclear membrane, which evidently represents the original nuclear membrane pushed out before the projecting protuberance or bud. There is no evidence that the buds are preformed and surrounded by a nuclear membrane (endogenous amitosis) within the mother nucleus. When the buds separate from the mother nucleus there remains no visible break in the membrane of the latter.

They arise from nuclei in which the intranuclear tension, judging from their wide meshwork and greatly increased amount of chromatin, is high. They appear to arise as the result of an expansive pressure within the nucleus and at the points of the nuclear surface where the membrane is thinnest and the cytoplasm is least dense; i. e., at the poles rather than at the lateral margins of the nucleus and the cell.

In the second type the nucleus breaks up into a number of buds of unequal size which overlap each other (fig. 7). It occurs in elongated as well as in round and oval nuclei. It differs from the first type in that the protuberant buds are much more irregular in size and shape, and the occurrence, in some instances, of definite multiple divisions of the karyosome preceding the budding process. It is probable that the budding process in this type is rapid and associated with high intra-nuclear tension. As in the first type, the nuclear membrane is pushed ahead of the developing buds, and there is no evidence of the formation of bands from the nuclear membrane dividing the nucleus up into segments within the original membrane (endogenous amitosis). There is no remnant or rest of the nuclear membrane surrounding the group of buds left when the latter separate.

The third type is characterized by the segmentation of the mother nucleus into a number (from 6 to 20 or more) small buds of about equal size. These may be thrown off from the mother nucleus graudally and in series (fig. 8) or the whole nucleus may break up simultaneously into these small buds (fig. 9). These buds are usually oval and overlap each other. They may appear clumped in a mass in the centre of the cell (fig. 9) or they may rapidly make their way towards the periphery (fig. 8). In this type, the process is probably a rapid one, due, perhaps, to sudden and marked increase of the intranuclear pressure in nuclei with uniformly thin nuclear membranes. In this type, multiple divisions of the karyosome previous to budding have not been observed. Here, again, the process is one of true budding (see fig. 8), without evidence of an intranuclear formation of daughter nuclei due to the splitting up of the nucleus into segments by ingrowths of the nuclear membrane (endogenous amitosis).

## Phenomena following Nuclear Budding.

These fall naturally into two classes, according as they concern nuclei and cytoplasm.

### a) Changes in the Nuclei following Nuclear Budding.

#### 1. Nuclear Buds.

Whatever the type of budding, the nuclear buds, except in cells with very dense or very fibrillar cytoplasm, such as cells of the epidermal type, tend to wander to the periphery of the cell (figs. 8, 10, 12, 13, 14, 15 and 16). They are usually round or oval and almost always relatively much less chromatic than the mother nucleus (fig. 6, 8 and 10). They usually contain from one to three small chromatic nucleoli or karyosomes and a variable number of small chromatin dots on the nuclear reticulum and the nuclear membrane. The nuclear buds, especially when of large size, may send off other crops of buds, which may again bud. This results in the presence in the cell of numerous buds of irregular shape and size and often connected by thick or thin strands of nuclear material (fig. 13). In addition to budding, nuclear buds may undergo amitosis by binary fission (figs. 11 and 12) or even normal mitosis (fig. 18).

Besides the above, the nuclear buds may undergo two other changes, degeneration and resorption (figs. 13, 14 and 15) and extrusion (fig. 16). Degenerated buds may shrivel and become hyperchromatic (fig. 15), fuse and be extruded (fig. 16), or after dissolution of their chromatic material, they may break up into larger and smaller deeply staining fragments (fig. 14). Resorption of nuclear buds occurs most frequently in large multinucleated giant cells. The chromatic material and the nuclear meshwork disintegrate and disappear, leaving a faintly staining rim of nuclear membrane as the sole trace of the nucleus. Fig. 13 shows three such nuclei in various stages of resorption.

### 2. The Mother Nucleus.

The mother nucleus is usually reduced in size and is commonly less hyperchromatic after budding. After budding, especially if the buds degenerate and are extruded, the mother nucleus may proceed to mitosis (figs. 15, 16 and 17). The mitoses occurring in such cells may be normal, without hypertrophied or otherwise degenerated chromosomes (figs. 15 and 16) or abnormal with hypertrophied chromosomes and even with multipolar figures (fig. 17).

After budding, and even while budding is in progress, the mother nucleus may divide by binary fission (figs. 11 and 12). Finally, after budding a very hyperchromatic mother nucleus may degenerate, sometimes with some of its buds (fig. 14).

## b) Changes in the Cytoplasm following Nuclear Budding.

There are reasons for thinking that there may take place a reorganization of cells after nuclear budding which results in a marked growth on the part of the cytoplasm. Giant cells containing nuclear buds are commonly much larger than those containing only a single hypertrophied giant nucleus. Following the wandering of nuclear buds to the periphery of the cell, the cytoplasm about such buds may protrude in such a manner as to furnish convincing evidence than there occurs a decided local growth of the cytoplasm about some of the buds (note the poles of the cell depicted in fig. 10). Cell division, with or without local growth of the cytoplasm about the buds, is of common occurence in cells with nuclear buds. After the wandering of the nuclear buds to the periphery of the cell, often small portions of the cytoplasm, each containing a single bud, or, more rarely, several buds, separate from the mother cell. In this case, the portion of cytoplasm about the bud which is to form the new cell is protruded from the mother cell (figs. 10, 12, 13 and 14); or, as is more rarely the case, the daughter cell containing a nuclear bud splits off as a narrow strip from the side of the cell (fig. 10). The frequent occurrence, in our tumor material, of this separation of daughter cells containing nuclear buds from giant cells with budded nuclei indicates that this is a common mode of cell multiplication in certain tumors. As may be seen by reference to the figures referred to, especially figs. 10 and 13, this process may give rise to well regulated cells with a nucleus plasma relation of normal or nearly normal proportions. Such daughter cells may be as well regulated as a type cell of the same tumor. As multinucleated giant cells in the process of giving off such daughter cells are often surrounded by small well regulated cells, which often contain normal mitotic or amitotic nuclear figures, it is evident that this is an important type of cell division and multiplication.

Our material furnishes evidence that there may take place occasionally within tumor cells, a type of intracellular division of the cytoplasm about nuclear buds similar to that occurring in certain protozoa, such as Tokophrya quadripartita, for instance. Perfectly developed and preserved cells of the type of tumor cells are not infrequently seen in giant cells containing budded nuclei. These cells lie in clear spaces within the mother cell. As, however, it has not been possible to trace this process in all its phases and in an absolutely convincing manner, and as it is difficult to exclude phagocytosis on the one hand and the wandering of one tumor cell into another on the other hand in explanation of these appearances, stress is not laid upon this point at the present time. The nuclear buds, though they usually wander to the periphery of the cell, are never symmetrically and equidistantly distributed in the cytoplasm, and the latter never breaks up into equal sized segments about the buds. The processes above described cannot, therefore, be directly compared with the multiple segmentation of nucleus and cytoplasm so commonly met with in the reproduction processes of certain protozoa.

The capacity of the cytoplasm to dispose of nuclear buds by resorption and extrusion has been described under the discussion of the fate of nuclear buds.

## The Mechanism of Nuclear Budding in Tumor Cells.

The type of nuclear budding described by us in tumor cells is neither preceded by nor accompanied by discernable action of any of the well known forms of attraction or division centres, such as centrosomes, attraction spheres and the like, resident or acting in the cytoplasm. Careful search has failed to disclose the presence of such bodies before, during or after the budding divisions. The cytoplasm of cells the seat of nuclear buds may contain centrosomes capable of active division function, however, for, as has been shown, after budding either the mother nucleus or the buds may undergo typical mitosis with centrosomes and spindles (figs. 15, 16, 17 and 18). But such attraction forces play, so far as we have been able to discover, no part in the divisions producing nuclear buds. Whatever its nature, the division energy controlling and determining nuclear budding seems to reside within the nucleus. In certain instances of nuclear budding, particularly in one tumor, a sarcoma, Dr. SCHULTZ and I have observed definite multiple divisions of the karyosome, with wandering of the daughter karyosomes from the centre towards the periphery of the nucleus and followed by a constriction or indentation of the nuclear membrane about those areas of the nucleus. This we have compared to the nucleocentrosome type of nuclear division, such as occurs in Euglena and in certain other protozoa. This process occurs especially in the type of multiple unequal budding of the nucleus (Type II).

But this explanation does not apply to the majority of instances of nuclear budding even of this type. As previously pointed cut, in most instances of nuclear budding there is evidence, as shown by the increased size of the nuclear meshwork and the high degree of hyperchromatism, that the intranuclear tension is markedly increased. In type I, which affords the best opportunity for the study of the mechanism of nuclear budding, the buds arise at the points where the nuclear membrane is thinnest and the cytoplasm least dense.

Consideration of these facts suggests that inmediately preceding budding, the hyperchromatic nucleus receives, through osmosis, a large accession of fluid from the cytoplasm. If this event were followed by excessive chemical activity within the nucleus, it is readily conceivable that the intra-nuclear tension might become so rapidly increased as to cause the extrusion of budding protuberances from the surface of the nucleus. In this case, the type of budding would be determined by the relation between the degree of pressure and the thinness and elasticity of the nuclear membrane.

Or again, changes in the surface tension of the nuclear membrane, possibly associated with changes in the cytoplasm, may perhaps play a determining or an adjuvant rôle in nuclear budding.

The budding divisions of the nucleus in tumors is not comparable to the process described by CHILD (1907 b) as fragmentation of the nucleus in the cytophores of the testes of Moniezia expansa and M. planissima in which, according to this author, new nuclei arise from certain areas in degenerating nuclei. Nor has it been possible to find in the nuclei of tumor cells the formation of smaller nuclei within the mother nucleus due to the ingrowth from the nuclear membrane of dividing strands, as described by CHILD (1907 a) in the developing sex cells of Moniezia and termed by him endogenous nuclear division.

The division of the nucleus and cytoplasm by budding described by us in tumor cells has its analogy in the various forms of budding met with in certain protozoa and described as budding with the formation of Schwärm or zoospores and as conitomy, but only the nuclear changes are comparable to the „Zerfallteilung“ or conitomy, for in the tumor cell the cytoplasm does not necessarily segment equally and at once as does that of the protozoan cell in this type o division.

The closest analogy to the budding divisions of tumor cells is that form met with in certain suctoria, especially that described by R. HERTWIG in Ephelota (Podophrya) gemmipara, whose band-like and somewhat horse-shoe shaped nucleus sends off a number of processes each connected with the mother nucleus by a thin strand of nuclear material and which make their way to the free surface of the cell, where a small knob-like protuberance of cytoplasm developes about each nuclear bud. These nucleated protuberances of cytoplasm finally separate from the mother cell as zoospores.

The types of nuclear budding described by us in tumor cells are of common occurrence in other pathological new growths characterized by rapid growth of tissue containing multinucleated giant cells. It is especially common in the giant cells of tuberculosis and of HODGKIN's disease.

## Relation of Nuclear Budding to Cell Regulation in Tumor Cells.

It has been pointed out that nuclear budding occurs in tumor cells with relatively large hyperchromatic nuclei, in cells from several to many times larger than the type cells and much larger than tumor cells in which normal mitoses are seen. It is met with, in other words, in cells with a nucleus plasma relation markedly in favor of the nucleus, notably in giant cells — a variety of cells which are in depression and to which mitosis as a division mechanism is debarred. These cells must, unless regulation is brought about through chromidiosis or nuclear resorption, either remain as resting cells, die in depression, or divide by amitosis. The ordinary type of amitosis, binary fission of the nucleus, does not seem to be often possible in such giant tumor cells. Therefore nuclear budding, with the opportunities it gives for reduction of nuclear material by degeneration, dissolution and extrusion of buds and for cell division, is apparently the only method of regulation open to such cells.

There is no doubt that the process of nuclear budding affords a simple and efficient method and means of cell regulation to cells in this condition.

This conclusion is based upon the following data:

1) The reduction in size and in chromatin content of the mother nucleus, which may be of such degree that it divides by mitosis.

2) The degeneration and extrusion of nuclear buds changes to a more or less complete degree an abnormal nucleus plasma relation to a normal one.

3) Nuclear budding is often followed by corresponding budding divisions of the cytoplasm, thus giving rise to well regulated daughter cells, which are capable of division by either mitosis or amitosis.

This type of cell division is especially common in tumors of moderately rapid and of rapid growth and for two reasons, 1) because it is in just such rapid rates of growth that cells tend to fall into depression from excessive over growth of nuclear material in proportion to cytoplasm, and 2) because this method of division and regulation, which is best market in cells of this type, is most condusive to rapid increase of tissue.

The extrusion of nuclear buds followed by mitosis of the mother nucleus has been likened by us [HOWARD (1910) and SCHULTZ], as being identical in principle with the maturation divisions of egg cells. For in both cases the nuclear material is reduced by the extrusion of nuclei; in the tumor cell depression is overcome and in the egg cell, in reality a depressed cell, the way is prepared for the proper mixing of the chromosomes of the male and female sex cells.

## Summary.

1) In certain depressed cells, usually giant cells, of some tumors of rapid, moderately rapid and occasionally those of slow growth, in which cell regulation by chromidiosis and by nuclear resorption is usually not in evidence, there occurs a special type of amitoses, nuclear budding.

2) This variety of nuclear budding is of three types: 1) one or more small buds spring from one or both poles of the mother nucleus, 2) breaking of the mother nucleus into numbers of overlapping buds of unequal size and 3) segmentation of the mother nucleus into a large number of small overlapping buds of equal size.

3) The nuclear buds tend to wander to the periphery of the cell. They may degenerate and become disintegrated, or be extruded by the cytoplasm; they may divide by mitosis or amitosis (by either binary fission or budding) or they may separate with portions of the cytoplasm from the mother cell, thus forming well regulated daughter cells capable of growth and of division by either mitosis or amitosis.

4) After reduction by budding division, the mother nucleus may undergo normal or abnormal mitosis, or may degenerate and disintegrate.

5) Nuclear division by budding is not brought about by any distinguishable division organ seated in the cytoplasm, but, with the exception of certain cases

in which the karyosome acts as a division organ of the nucleo-centrosome type, the process is due apparently to a rapid increase in the intra-nuclear tension.

6) Nuclear budding in tumor cells represents a reversion on the part of these cells to a primitive type of nucleus and cell division common among certain protozoa.

7) Nuclear budding in tumor cells affords a ready and simple means of cell regulation and of rapid division and multiplication among such cells.

8) The degeneration and extrusion of nuclear buds followed by mitosis of the mother nucleus in tumor cells is, in principle, comparable to the maturation divisions of egg cells.

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## Description of figures.

All the drawings were made with the Spencer Camera lucida, Zeiss 2 mm, oil immersion objective, No. 6 compensating ocular, and tube length 160 mm, giving thus a uniform magnification of 1480. The drawings are all from sections stained with DELAFIELD's haematoxylin and eosine.

Fig. 1. Type cell. A normal cell with a well regulated nucleus plasma relation. Tumor 11.

Fig. 2. A cell with a large hyperchromatic nucleus and a marked upset of the nucleus plasma relation in favor of the nucleus. The increased size of this cell is due mainly to the overgrowth of the nucleus. Tumor No. 4.

Fig. 3 and 4. Cells dead from depression. In fig. 3, the chromatin is dissolved throughout the nucleus, the nuclear structure is obscured, the cytoplasm is completely structureless and stains very deeply with eosine. In fig. 4 the hyperchromatic and vacuolated nucleus is disintegrating; the cytoplasm in general is hyaline but shows large vacuoles at one pole. Tumor No. 11.

Fig. 5. A large cell whose hypertrophied and hyperchromatic nucleus has divided by binary fission. Tumor No. 11.

Fig. 6. A small giant cell whose markedly hypertrophied and hyperchromatic nucleus is sending off small buds from one pole, — nuclear budding of the first type. Tumor No. 11.

Fig. 7. A giant cell whose nucleus is undergoing multiple budding with the formation of buds of unequal size, — nuclear budding of the second type. Tumor No. 11.

Fig. 8. A giant cell whose nucleus is sending off multiple buds of about equal size in series. Tumor No. 4.

Fig. 9. A giant cell with segmentation of the nucleus into multiple buds of equal size, — nuclear budding of the third type. Tumor No. 11.

Fig. 10. A very large giant cell with numerous buds wandering to the periphery of the cell. The mother nucleus, lying near the centre of the cell, is in process of budding at one pole, — nuclear budding of the first type. At each pole and at the lateral margins of this cell, daughter cells are arising by separation of portions of cytoplasm containing nuclear buds. Tumor No. 11.

Fig. 11. A giant cell in process of division. The mother nucleus is giving off a small bud at one pole. Near the opposite pole at one lateral margin of this nucleus and connected with it by a band of nuclear material, there has arisen a large nuclear bud which, while giving rise to secondary buds, is dividing by binary fission. Tumor No. 11.

Fig. 12. A giant cell whose mother nucleus, after giving off buds and while still forming buds, is dividing by binary fission. About another nuclear bud at

one pole of the cell, the cytoplasm is dividing to form a daughter cell. Tumor No. 11.

Fig. 13. A huge giant cell, containing numerous large and small nuclear buds, some of which are giving rise to a series of buds. There are three nuclear buds in various stages of dissolution and resorption. At one pole of the cell the cytoplasm is splitting off about two nuclear buds with the production of two daughter cells. The cytoplasm of this cell must have grown rapidly after nuclear budding began. Tumor No. 11.

Fig. 14. A giant cell in which after nuclear budding there has occurred degeneration of the mother nucleus and three nuclear buds. At one pole of the cell a daughter cell is in process of formation by the separation of a portion of the cytoplasm about a nuclear bud. Tumor No. 11.

Fig. 15. A cell showing degeneration of two nuclear buds and the occurrence of normal mitosis of the mother nucleus after nuclear budding. Tumor No. 4.

Fig. 16. A cell with the mother nucleus in normal mitosis after nuclear budding and degeneration and extrusion of the buds. Tumor No. 4.

Fig. 17. A cell with multipolar mitosis of the mother nucleus occurring after nuclear budding. Tumor No. 4.

Fig. 18. A giant cell with a somewhat hyperchromatic mother nucleus and three nuclear buds one of which is in mitosis. Tumor No. 4.

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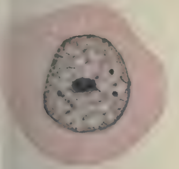

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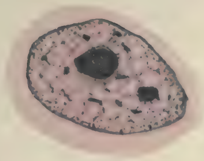

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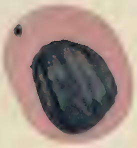

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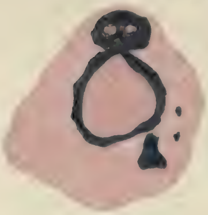

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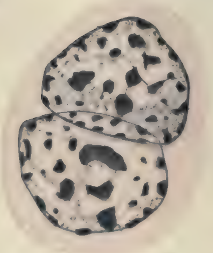

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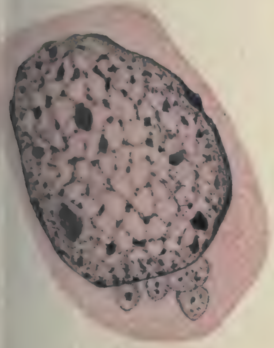

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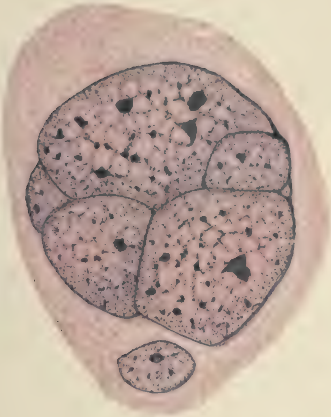

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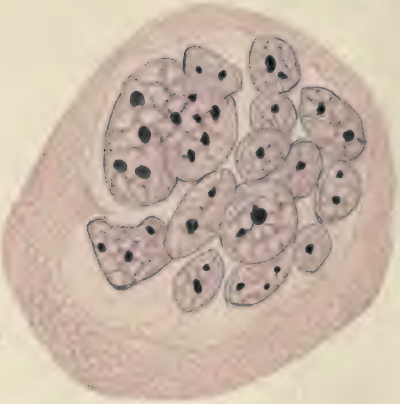

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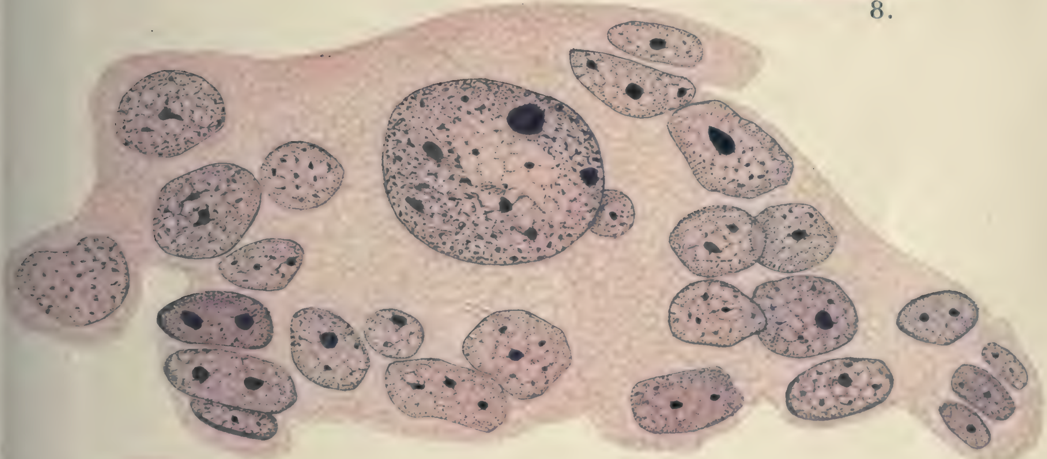

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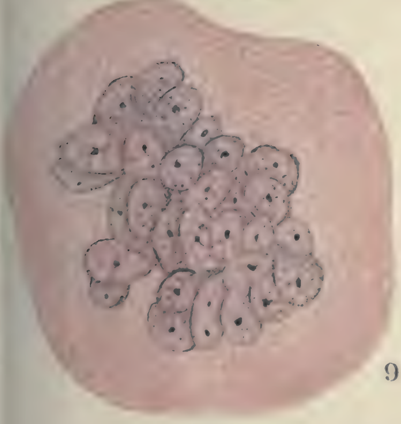

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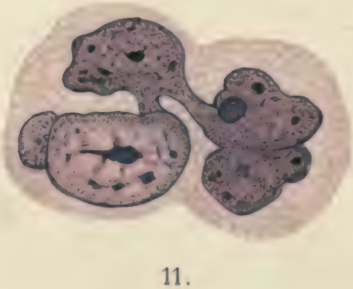

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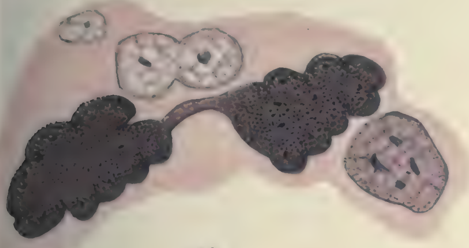

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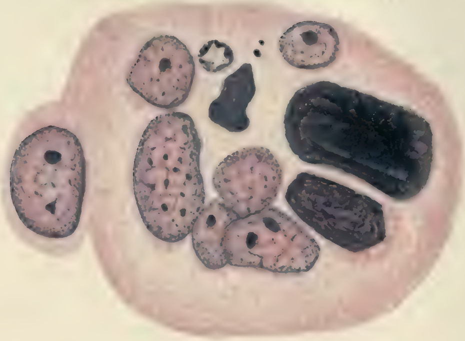

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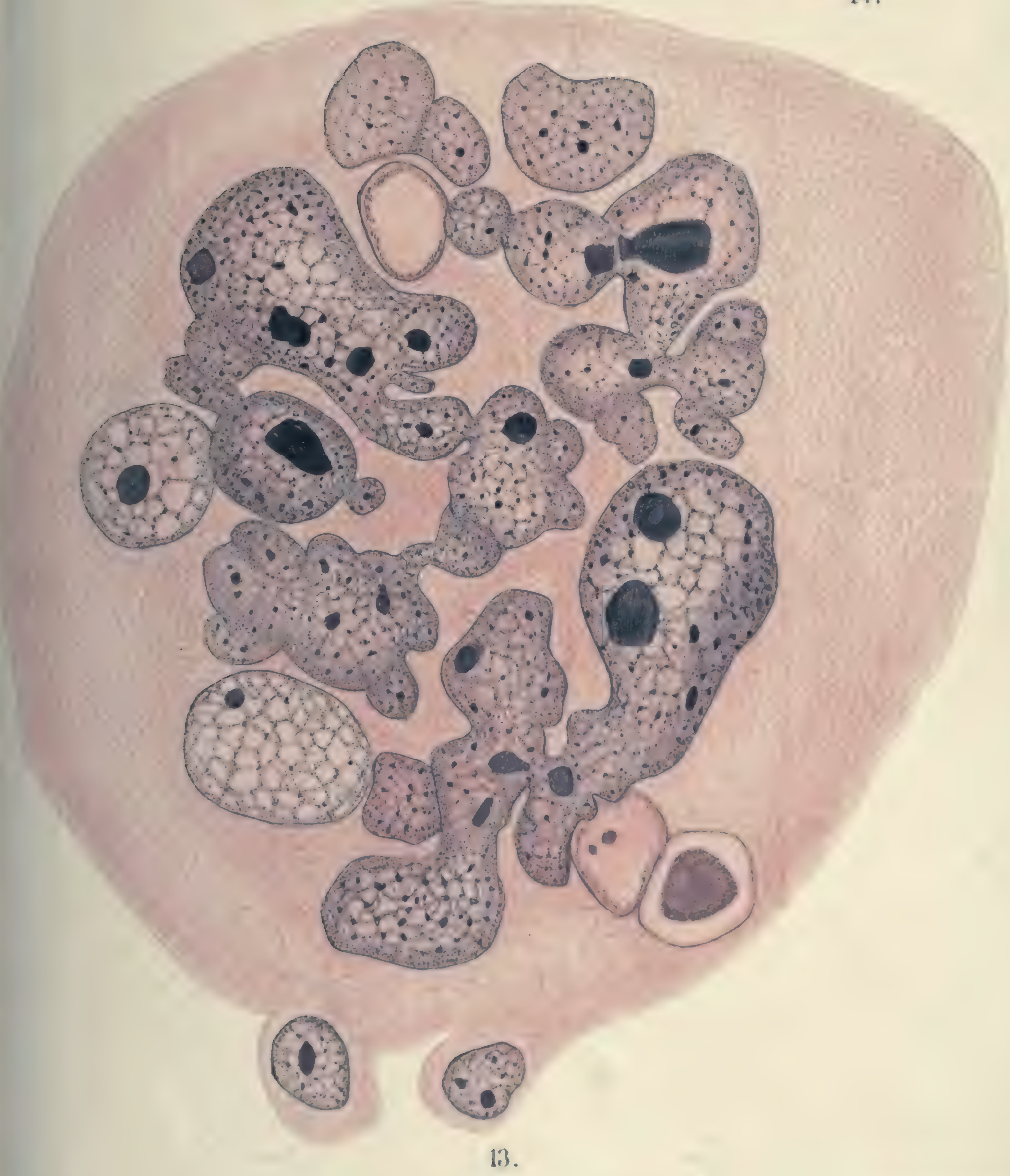

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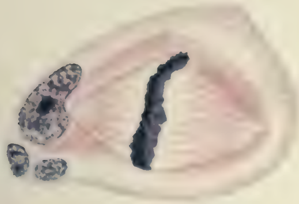

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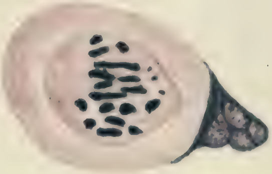

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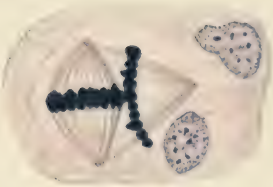

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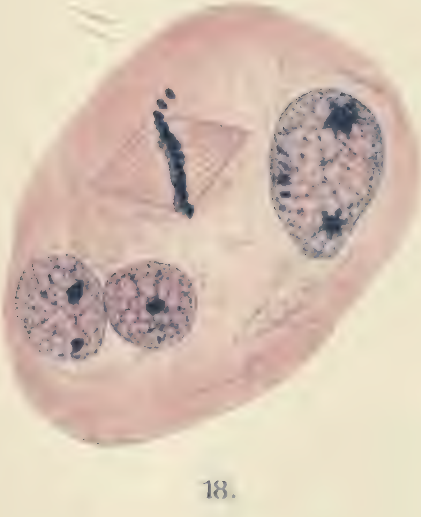

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